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RENAL AMYLOIDOSIS: A REVIEW OF 12 CASES*

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ORIGINALLY called "lardaceous disease" by Rokitansky in 1842,[1] amyloidosis frequently involves the kidneys. The deposition of amyloid material in the glomeruli leads to an increase in permeability with resulting proteinuria and, in many cases, pitting edema of the extremities. Renal involvement in secondary amyloidosis is two to three times more common than in primary amyloidosis, but the clinical manifestations are similiar.[2-4] The diagnosis, which is suggested by the onset of proteinuria and the development of the nephrotic syndrome, is more easily recognized in the secondary form of the disease. Primary amyloidosis has in the past often been confused with membranous glomerulonephritis.[2]

With the advent of antibiotics and other advances in medical therapy the number of cases of amyloidosis secondary to tuberculosis and chronic suppurative infections has decreased.[1, 5] Although other initiating causes of secondary amyloidosis are numerous, its association with rheumatoid arthritis and regional enteritis is appearing in the literature in increasing frequency.[5, 6]

The following is a report of 12 cases of renal amyloidosis, six of the primary and six of the secondary types; the association of renal vein thrombosis in three of the cases is of particular interest.

CASE 1.—E.K. (Q.M.V.H., No. AN-33134), a white male, was born in 1916; he was hospitalized first in 1949 because of an episode of fever, diarrhea and abdominal pain. From 1952 until 1960, he had recurrent episodes of diarrhea, tenesmus, abdominal pain, weight loss and general malaise; in 1952 and 1956 he had associated pain, swelling and tenderness in multiple joints. Sigmoidoscopy in 1952 revealed two ulcers in the sigmoid colon, and a diagnosis of idiopathic ulcerative colitis was made.

In 1957, the mucosa of the lower bowel was normal by sigmoidoscopic examination; however, a right lower quadrant abdominal mass was discovered at this time. The patient was subjected to an abdominal laparotomy during which a right hemicolectomy was performed. The mass, which had to be dissected free of the right ureter, involved the terminal ileum and cecum. The pathological diagnosis of regional ileitis was made after examination of tissue from the lesion. During this period in hospital 300-600 mg. % protein was present in the urine.

He was admitted to hospital again in September 1957 for investigation of this proteinuria. An intravenous pyelogram demonstrated narrowing at the left pelviureteric junction. A left ureteroplasty was performed during which a stricture 1½" long was excised. Examination of tissue obtained by a biopsy of the kidney during the operation gave evidence of amyloidosis and pyelonephritis.

In 1958 he was admitted to hospital because of diarrhea and abdominal pain. A barium enema was performed and its appearance suggested the presence of extensive ulcerative colitis. On physical examination, the blood pressure was 135/80 mm. Hg and pitting edema of the extremities was present. The urinary sediment contained 10-15 white blood cells, one or two red blood cells per high power field and frequent leukocyte casts. The quantitative determination of urinary protein gave values which ranged from 5 to 10 g./24 hr. Renal function studies showed a maximum specific gravity of 1.029 and an endogenous creatinine clearance of 100 ml./min. The blood urea nitrogen determination was 11.7 mg. %, the serum cholesterol was 380 mg. % and the Congo Red test showed that 66% of the dye was removed from the blood in one hour. The serum protein electrophoresis gave the following values: albumin 0.87 g. %, and alpha$_2$ globulin 1.01 g. %.

This patient had been treated with corticosteroids intermittently since 1958 and in September 1960 he was cushingoid in appearance with a round facies and supraclavicular fat pads. He had moderate dependent edema and severe muscle wasting but there was no change in his renal function.

CASE 2.—M.C.P. (M.G.H., No. 127004), a white female, was born in 1934; she was hospitalized in 1950 and the diagnosis of pulmonary tuberculosis was made. From 1953 to 1959 she was admitted to hospital repeatedly for treatment of active pulmonary tuberculosis. In March 1959, she developed exertional dyspnea and dependent edema. Protein was excreted in the patient's urine at this time and quantitatively the loss was about 8 g./24 hr. (Esbach). Improvement in her

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symptoms followed the imposition of salt restriction and the use of diuretics and digitalis. In February 1960, when she was admitted to the Montreal General Hospital, radiographic examination of the chest showed complete destruction of the left lung. The patient's blood pressure was 110/70 mm. Hg and pitting edema of the legs was noted. The urinary sediment contained 2-4 leukocytes and 1-2 erythrocytes per high power field, occasional oval fat bodies, hyaline and granular casts. The quantitative determination of urinary protein gave a value of 1.7 g./24 hr. Renal function studies showed a maximum specific gravity of 1.023 and the phenosulfonphthalein excretion was 65% in 60 minutes. The blood urea nitrogen was 10.7 mg. %, the serum cholesterol was 338 mg. %, and the Congo Red test showed that 70% of the dye was removed from the blood in one hour. By electrophoretic examination of the serum proteins the albumin was 1.3 g. % and the alpha$_2$ globulin fraction was 0.90 g. %. A renal biopsy confirmed the diagnosis of amyloidosis.

In May 1960, the left lung was removed. The surgical specimen was a markedly shrunken and deformed lung. Irregular thickening of the pleura was present and on the posterior-inferior aspect of the left lower lobe there was an irregular cavity 8 cm. in its maximum diameter.

On a follow-up examination in January 1961, this patient had no dyspnea and there was no evidence of edema on physical examination. The quantitative determination of the urinary excretion of protein was 1.8 g./24 hr.; the blood urea nitrogen was 16 mg. %, the serum cholesterol was 264 mg. % and the endogenous creatinine clearance was 84 ml./min.

CASE 3.—A.A. (R.V.H., No. 009026), a white female and a sister of the patient G.C. (Case 4), was born in 1914. In childhood she suffered from recurrent throat infections, bilateral otitis media, a cerebral abscess and rheumatic fever, and since 1927, she had a recurrent dermatitis which is urticarial in type. In April 1957, the patient developed exertional dyspnea and dependent edema; on physical examination, the blood pressure was 120/80 mm. Hg, diastolic and systolic murmurs were heard over the apex of the heart and a blotchy maculopapular erythematous rash was noted. The urinary sediment showed 3-4 leukocytes and 1-2 erythrocytes per high power field, and also occasional oval fat bodies, and hyaline and granular casts. A quantitative determination of the urinary excretion of protein was 6.7 g./24 hr. Renal function studies revealed a maximum specific gravity of 1.024, the excretion of phenosulfonphthalein was 34.5% in 15 minutes, and the endogenous creatinine clearance was 111 ml./min. The patient's blood urea nitrogen was 13.3 mg. %; the serum cholesterol was 273 mg. % and the total serum protein 6.67 g. %. The Congo Red test showed that 64% of the dye was removed from the blood in one hour. A renal biopsy established the diagnosis of amyloidosis.

In February 1958, the patient had a urinary tract infection which responded to treatment with chloramphenicol. In May 1959, she was admitted to hospital with complaints of nausea, vomiting and weight loss, and enlargement of the liver was noted during examination of the abdomen. At this time the nonprotein nitrogen was 98 mg. %, and the serum cholesterol was 183 mg. %; by electrophoretic examination, the serum proteins were: albumin 1.44 g. %, alpha$_2$ globulin 1.94 g. %.

CASE 4.—G.C. (R.V.H., No. 013443), a white female and a sister of the preceding patient A.A. (Case 3), was born in 1918. In 1956, a thyroid nodule was excised from this patient which revealed evidence of amyloidosis on microscopic examination. At this time history was obtained of a recurrent skin rash that had been present since 1934 and of recurrent dependent edema of the lower extremities since 1954. Two years before admission the patient developed weight loss and vague abdominal complaints, and a radiographic examination of the stomach demonstrated an ulcer on the lesser curvature.

The complaints of exertional dyspnea, weakness and fatigability began just before admission to hospital in 1956. The patient's blood pressure was 140/90 mm. Hg; she had pallor and edema of the face, an apical systolic murmur, an enlarged liver and a nodule of the thyroid gland.

The urinary sediment showed 5-10 leukocytes per high power field, frequent hyaline and granular casts, occasional oval fat bodies, occasional fatty casts, and 3.5 g. of protein in the urine in 24 hr. (Esbach). Renal function studies revealed a maximum specific gravity of 1.010, the excretion of phenosulfonphthalein of 11% in 15 minutes, and an endogenous creatinine clearance of 58 ml./min. The blood urea nitrogen was 30 mg. %, the serum cholesterol was 262 mg. %, and the total serum protein was 7.2 g. %.

In March 1960, she was admitted to hospital because of the complaints of nausea, vomiting and weight loss. The blood pressure was 190/110 mm. Hg, the thyroid gland was enlarged bilaterally, and the liver was enlarged. On quantitative determination the loss of protein in the urine was 12.3 g./24 hr.; there was evidence of gross impairment of renal function; the phenosulfonphthalein excretion was less than 1% in 15 minutes, the urea clearance was 5.5 ml./min. and the nonprotein nitrogen was 115 mg. %. By electrophoresis the serum protein values were: albumin 3.3 g. %, and alpha$_2$ globulin 1.10 g. %.

In July 1960, she was admitted again with marked weight loss and general malaise. Her condition deteriorated rapidly and she died during that month. Postmortem examination revealed generalized amyloidosis, bilateral chronic pyelonephritis and left ventricular hypertrophy.

CASE 5.—P.S. (Q.M.V.H., No. AB-17970), a white male, born in 1913, was admitted to hospital in 1946 and the diagnosis of pulmonary tuberculosis was made. An artificial pneumothorax was done and was complicated by the development of empyema. In May 1949, the tuberculosis was said to be arrested; however, bilateral reactivation occurred in 1953. In December 1954, a two-stage thoracoplasty was carried out, but this in turn was complicated by the development of staphylococcal infection in the wound. Trace amounts of protein were present in the urine intermittently during this period.

In 1955, the complaints of weight loss and abdominal pain led to radiographic examination which demonstrated a gastric ulcer. From 1955 to 1957, this patient had persistent pain in the left chest. The blood pressure was 140/90 mm. Hg, the liver was enlarged and the urine contained protein and leukocytes on repeated examination. The empyema, which had recurred intermittently since 1946, was cured by open drainage in 1958.

Examination of the urinary sediment in 1957 revealed 4-5 leukocytes and erythrocytes in each high power field, numerous oval fat bodies, hyaline and granular casts, and frequent fatty casts. Quantitative determinations of urinary protein losses ranged from 15.3 to 23.2 g./24 hr. Renal function studies showed a maximum specific gravity of 1.018 and a phenosulfonphthalein excretion of 35% in 15 minutes. The blood urea nitrogen was 24.7 mg. %, the serum cholesterol was 296 mg. %, and the Congo Red test showed that 99% of the dye was removed from the blood in one hour. By electrophoresis the serum protein was: albumin 2.25 g. % and alpha$_2$ globulin 1.18 g. %.

In January 1958, the patient developed dependent edema and the complaints of an increasing cough, recurrent syncope and mental confusion; the blood pressure was 175/105 mm. Hg. His clinical course was steadily downhill and ended in his death. Postmortem examination revealed amyloidosis of the liver, adrenals, spleen and kidneys; there was atelectasis of the left lung, and left ventricular hypertrophy.

CASE 6.—R.B. (R.V.H., No. 20477), a white male, born in 1905, was first known to have renal disease in 1947, when protein was found in the urine. An intravenous pyelogram was done soon after and was normal. In 1950, the diagnosis of "dry nephritis" was made elsewhere and therapy with corticosteroids was begun. In 1950, he had the following findings: protein in the urine, a serum protein determination of 3 g. % and a serum cholesterol of 800 mg. %. The patient did not have exertional dyspnea and dependent edema was not present.

In February 1957, he was admitted to the Royal Victoria Hospital because of a long-standing history of recurrent abdominal pain; this complaint had been investigated on a number of occasions without result. On examination, there was evidence of a well-developed Cushing's syndrome secondary to corticosteroid therapy; he had moon facies, supraclavicular fat pads, and sacral and ankle edema, and the blood pressure was 185/100 mm. Hg. Examination of the urinary sediment revealed rare leukocytes, and rare erythrocytes per high power field, occasional oval fat bodies, a moderate number of hyaline and granular casts, and occasional fatty casts. A quantitative determination of the urinary protein loss was 3 g./24 hr. Renal function studies showed a maximum specific gravity of 1.014, a phenosulfonphthalein excretion of 43.6% in 15 minutes, and an endogenous creatinine clearance of 75.4 ml./min. The blood urea nitrogen was 23.6 mg. %, the serum cholesterol was 134 mg. % and the total protein was 5.42 g. %. By electrophoresis serum protein was: albumin 1.68 g. % and alpha$_2$ globulin 1.66 g. %. A renal biopsy established the diagnosis of amyloidosis. The radiograph of the chest and the intravenous pyelogram were within normal limits. The electrocardiogram was normal.

In April 1957, he suffered an attack of lower abdominal pain which was accompanied by a low-grade fever. Dependent edema and persistent albuminuria were present and the endogenous creatinine clearance was 62 ml./min. A sigmoidoscopy and barium enema demonstrated several polyps in the colon. On withdrawal of steroid therapy, the patient became normotensive.

In November 1957, he was admitted because of abdominal discomfort; the blood pressure was 110/70 mm. Hg; there was only a trace of dependent edema and the renal function studies were unchanged. On November 18, 1957, an exploratory laparotomy was done and three sigmoid polyps were excised. During the postoperative period, he developed nausea, vomiting, abdominal pain and distension, and oliguria. The renal function continued to deteriorate and he died in uremia on December 22, 1957. A postmortem examination revealed widespread primary amyloidosis and bilateral renal vein thrombosis.

CASE 7.—P.G.C. (Q.M.V.H., No. AK-15807), a white male, born in 1893, was admitted to the Queen Mary Veterans Hospital in April 1957 with a 12-month history of exertional dyspnea, polydipsia and nocturia. He had had dependent ankle edema for one month. Examination revealed a blood pressure of 160/90 mm. Hg, an apical mid-systolic murmur and moderately severe pitting edema of the lower extremities. Examination of the urinary sediment showed 3-4 leukocytes, 1-2 erythrocytes and 2-3 oval fat bodies per high power field; there were also many hyaline and granular casts, very frequent fatty casts and occasional leukocyte casts. Quantitative urinary protein determinations ranged from 6 to 7.5 g./24 hrs. Renal function studies revealed a maximum specific gravity of 1.015, a phenosulfonphthalein excretion of 2% in 15 minutes, and an endogenous creatinine clearance of 33.7 ml./min. The blood urea nitrogen was 31.2 mg. %, the serum cholesterol was 395 mg. %, and by electrophoresis the serum protein was: albumin 2.75 g. % and alpha$_2$ globulin 1.29 g. %. The Congo Red test showed that 80% of the dye was removed from the blood in one hour. The renal biopsy showed nephrosclerosis and was compatible with glomerulonephritis.

The patient was placed on salt restriction with a decrease in the dependent edema and dyspnea. In July 1957, his blood pressure was 155/90 mm. Hg. In November 1957, he had a sudden onset of diarrhea, vomiting, abdominal distension and fullness, accompanied by a marked increase in his exertional dyspnea and dependent edema. Examination revealed massive dependent edema to the level of the lower abdominal wall. Ascites was present and the liver was grossly enlarged. A liver biopsy showed evidence of amyloidosis. The renal biopsy was reviewed and the diagnosis of amyloidosis, which had been previously overlooked, was confirmed. Intensive therapy with salt restriction, diuretics and eventually corticosteroids did not bring about any improvement. He died in January 1958. A postmortem examination showed amyloidosis of the liver, kidneys, thyroid, pancreas and spleen.

CASE 8.—V.R. (M.G.H., No. 000808), a white female, born in 1900, was admitted to hospital in May 1959 for the investigation of proteinuria. The patient had a 10-year history of rheumatoid arthritis; the disease process began in the hands and went on to involve the wrists, toes, ankles, knees, and shoulders. She had been treated with salicylates, phenylbutazone, chloroquine, gold, physiotherapy and corticosteroids. Trace amounts of protein had been noted in the urine in 1957; however, massive proteinuria did not develop until the period between August and October of 1958. Dependent edema was first noted in 1956 but was more marked and more persistent at the time of her admission to hospital.

In May 1959, examination revealed a blood pressure of 160/90 mm. Hg, an aortic systolic murmur and

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moderate pitting edema of the ankles. Changes in the joints typical of rheumatoid arthritis were present and were most marked in the hands. A radiograph of the chest showed demineralization of the vertebrae only; an intravenous pyelogram and the electrocardiogram were normal. Examination of the urinary sediment showed 1-2 leukocytes per high power field, scattered oval fat bodies, very many hyaline casts and the occasional leukocyte cast. Quantitative urinary protein determinations ranged from 1.8 to 2.3 g./24 hr. The maximum specific gravity was 1.025, the blood urea nitrogen was 10 mg. %, and the serum cholesterol was 194 mg. %. By electrophoresis the serum protein was: albumin 2.1 g. %, and alpha$_2$ globulin 1.4 g. %. The Congo Red test showed that 33% of the dye was removed from the blood in one hour. A renal biopsy confirmed the diagnosis of amyloidosis.

In January 1961, during a follow-up examination, this patient complained of joint pain and swelling which was migratory in nature. There was minimal pitting edema of the ankles. Renal function studies showed an endogenous creatinine clearance of 83.7 ml./min., and a quantitative urinary protein of 2.4 g./24 hrs.

CASE 9.—J.K.G.I. (Q.M.V.H., No. AP-40777), a white male, born in 1889, was admitted to the Queen Mary Veterans Hospital for the first time in March 1958. He denied any previous illnesses and complained of exertional dyspnea, orthopnea, nausea, vomiting and abdominal pain, of two weeks' duration. On examination the blood pressure was 130/80 mm. Hg, dependent edema and changes in the radiograph of the chest compatible with diffuse obstructive emphysema were present. The urinary sediment showed many oval fat bodies and numerous hyaline and granular casts. The maximum urinary specific gravity was 1.017 and the urinary protein ranged from 380 to 640 mg. %. The blood urea nitrogen was 14.2 mg. %, the serum cholesterol was 240 mg. %, and the albumin to globulin ratio was 2.94/2.64. Following the use of diuretics, salt restriction and digitalis, remarkable improvement occurred and he was discharged from hospital.

In March 1959, he was admitted to hospital again with the complaints of nausea, vomiting and urinary frequency. Examination revealed a blood pressure of 170/90 mm. Hg, a right pleural effusion and evidence of both right and left ventricular failure. There was massive proteinuria, the blood urea nitrogen was 85.8 mg. % and the serum cholesterol was 127 mg. %. No improvement took place following treatment by salt restriction, diuretics and digitalis; the patient died in terminal pulmonary edema one week after admission to hospital. The postmortem examination revealed amyloidosis of the adrenals, spleen, thyroid and kidneys; and bilateral renal vein thrombosis, both recent and old, was noted. There was an associated pulmonary edema and right hydrothorax.

CASE 10.—A.F. (M.G.H., No. 034976), a Negress, born in 1938, was admitted to the Montreal General Hospital for the first time in May 1958, complaining of weakness, lethargy, easy fatigability, and a mass on the right side of her neck. The cervical mass had come to her attention first in 1956, and in 1957 she complained of fainting when assuming the upright position. Biopsy of the right submandibular mass led to the recognition of a benign carotid body tumour. A lymph node removed at the same time was described as "non specific lymphadenitis". The urine showed traces of protein.

She was re-admitted to the Montreal General Hospital in February 1960, complaining of continued weakness and fatigability, diarrhea, which was occasionally bloody, and abdominal pain. During this period in hospital, the patient developed persistent nausea and vomiting as well as pretibial and sacral pitting edema. On examination she was emaciated and pale, and appeared chronically ill. The blood pressure was 96/60 mm. Hg; and a right submandibular mass 2 cm. in diameter was present. On abdominal examination there was a right upper quadrant mass; and on sigmoidoscopy the mucosa was edematous and inflamed with small ulcerations at 11 cm. The urinary sediment showed 3-4 leukocytes and 1-2 erythrocytes per high power field, scattered oval fat bodies, frequent hyaline and granular casts, and occasional waxy casts. The quantitative urinary protein was 14.92 g./24 hr. and the maximum urinary specific gravity was 1.030. The blood urea nitrogen was 10 mg. % and the serum cholesterol 221 mg. %. By electrophoresis the serum protein was: albumin 0.2 g. % and alpha$_2$ globulin 1.1 g. %. She became progressively more uremic and died on February 23, 1960. A postmortem examination revealed widespread primary amyloidosis; the left kidney weighed 390 g. and the right kidney 325 g.

CASE 11.—T.S. (M.G.H., No. 038217), a white male, born in 1922, had arthritis in 1944, at which time he complained of recurrent pain and swelling of the right ankle, right wrist and both shoulders. In 1948, he had back pain, and radiographic examination of his spine and pelvis revealed partial fusion of the right sacroiliac joint; a diagnosis of ankylosing spondylitis was made. From 1950 to 1954, he continued to have migratory joint pain and during this period had two episodes of iritis. In 1956, the patient had marked deformity and limitation of movement, most marked in the knees, hips and spine. The urine contained trace amount of protein and the Congo Red test showed that 51% of the dye was removed from the blood in one hour. In 1958, he developed dependent edema. Examination of the urinary sediment showed 3-5 leukocytes and 3-5 erythrocytes per high power field, many oval fat bodies, hyaline and granular casts, and the occasional leukocyte cast. Renal function studies showed a maximum specific gravity of 1.011, a phenosulfonphthalein excretion of 5% in 15 minutes, and a urea clearance of 28%. Quantitative urinary protein determinations ranged from 7 to 9 g./24 hr. The blood urea nitrogen was 30 mg. %, the serum cholesterol was 230 mg. %, and by electrophoresis the serum protein was: albumin 0.4 g. % and alpha$_2$ globulin 1.4 g. %.

Dependent edema had been noted for the first time in April 1958, and by November of the same year it had become generalized. The patient was very cachectic and developed severe burning retrosternal and abdominal pain. The uremia became progressively worse, and he died after aspiration following moderately severe hematemesis. A postmortem examination revealed amyloidosis of the adrenals and kidneys, lesser involvement of the spleen, and involvement of the blood vessels of the liver.

CASE 12.—E.McC. (G.D.H., No. 5986), a white male, born in 1914, had pulmonary tuberculosis in 1948. He was treated by means of a two-stage thoracoplasty the same year and in 1953, with a pneumoperitoneum, streptomycin and para-aminosalicylic acid. The patient continued on this therapy but in March 1955 developed dyspnea, hemoptysis and weight loss. Examination revealed a blood pressure of 90/62 mm. Hg, chest deformity, decreased breath sounds over the right upper lobe and moist rales over the left upper lobe. A radiograph of the chest showed a large cavity 3 x 4 cm. in the right upper lobe.

In the summer of 1955, he developed heavy proteinuria, and on examination in March 1956, he had massive dependent edema, an enlarged liver and ascites. The maximum urinary specific gravity was 1.030 and the urinary protein was approximately 14 g./day. The blood urea nitrogen was 20 mg. %, the serum cholesterol was 252 mg. %, and the serum albumin was 1.0 g. %. The Congo Red test showed that 64% of the dye was removed from the blood in one hour. A renal biopsy, done in August 1956, confirmed the diagnosis of amyloidosis.

There was no improvement after a continuation of therapy which included streptomycin, para-aminosalicylic acid, isonicotinic acid hydrazide, salt restriction, diuretics and digitalis. The patient died in November 1956. A postmortem examination revealed marked amyloidosis of the kidneys, adrenals and spleen.

DISCUSSION

These 12 cases of renal amyloidosis, six primary and six secondary, include seven male and five female patients who range in age at diagnosis from 22 to 70 years, with a mean age of 44 years. Eight of the patients have died, seven of them within one to 50 months following diagnosis with a mean of 14.5 months; one died before the diagnosis was made. Four patients are still living, 24 to 49 months following diagnosis, a mean of 37.7 months; of this latter group three have secondary amyloidosis and one has primary amyloidosis.

The equal distribution of the cases between the primary and secondary forms draws attention to the relative decrease which has occurred in the number of cases of secondary amyloidosis. At the time of diagnosis, all patients with the secondary form of the disease had a long-standing history of the initiating cause for periods from 8 to 14 years. In six cases of the secondary form, tuberculosis was present in three, arthritis in two and regional enteritis in one. Of the three patients with tuberculosis, one (Case 2) had a left pneumonectomy two months after the diagnosis of secondary amyloidosis. The surgical specimen was a markedly shrunken and deformed lung with a large irregular cavity in the lower lobe. One patient (Case 5) had a long-standing recurring empyema and the other (Case 12) had bilateral apical cavitations with bronchiectasis of the right middle and left upper lobes at autopsy. Of the two patients with arthritis, one (Case 11) had ankylosing spondylitis with peripheral joint involvement and the other (Case 8) had rheumatoid arthritis and osteoarthritis. The remaining patient (Case 1) is believed to have ulcerative colitis and regional ileitis. Amyloidosis in association with ulcerative colitis has been reported only six times in the literature.[6] It should be noted that in this patient with ulcerative colitis, there has never been any evidence of fistula formation or peri-intestinal suppuration, one of the possible initiating factors in the amyloidosis associated with this disease.[7]

TABLE I.—THE PRESENTING COMPLAINTS IN 12 CASES OF RENAL AMYLOIDOSIS

Dependent edema	10
Exertional dyspnea	7
Abdominal pain	3
Nausea and/or vomiting	4
Diarrhea	3
Joint pain	3
Weight loss	2

As noted in Table I, the most common present symptoms were dependent edema and exertional dyspnea. Gastrointestinal complaints were common and non-specific in nature, and although invariably present in the end stages of renal failure, they were also common prior to the development of uremia. Physical examination at the time of diagnosis revealed dependent edema in nine cases, an enlarged liver in three, and a palpable kidney in one. Arterial hypertension is said to be uncommon in amyloidosis.[8, 9] Loughridge[2] and others[10] have remarked on the misleading nature of this belief. Nevertheless, in a recent review of 15 cases of renal amyloidosis, hypertension was noted in only one case;[3] in another series hypertension was noted in six of the 11 cases reviewed.[10] In the present series, two patients (Cases 4 and 8) had both systolic and diastolic hypertension (a blood pressure $>$ 150/90 mm. Hg), two (Cases 7 and 9) had only systolic hypertension, one (Case 5) developed hypertension as his illness progressed and one (Case 6) had hypertension while on corticosteroid therapy. Of the two patients with both systolic and diastolic hypertension, one (Case 4) is dead and had left ventricular hypertrophy at autopsy and the other (Case 8) is living but has grade I hypertensive retinopathy.

Radiological investigation of the genito-urinary system was carried out in all cases; of seven intravenous pyelograms, five (Cases 2, 3, 6, 8 and 12) were within normal limits, one (Case 1) showed dilatation of the superior major and minor calyces on the left and dilatation of the renal pelvis and narrowing of the ureter on the right, and one (Case 4) showed a discrepancy in kidney size and decreased excretion on the right. Two retrograde pyelograms (Cases 5 and 10) were within normal limits and the abdominal films (Cases 7, 9 and 11) revealed no abnormalities in renal size or contour, although visualization was inadequate in one study (Case 9).

The presence of edema led fairly quickly to the investigation of the urinary tract. Protein was

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present in the urine of every case. When measured, a loss of more than 5 g. of protein, with a mean of 10 g./day, was demonstrated in 10 of the 12 cases. Two patients had a loss of less than 4 g./day but developed a decrease in serum albumin and dependent edema (Cases 2 and 8).

In all cases the examination of centrifuged urinary sediment showed the presence of hyaline and granular casts, and fat either in the form of oval fat bodies, fatty casts or both. Pyuria, more than five leukocytes per high power field, was present in three patients (Cases 1, 4 and 9). Of these, two had pyelonephritis, in one (Case 1) the diagnosis was established by biopsy of the kidney and was confirmed at autopsy in the other (Case 4); at autopsy the remaining patient (Case 9) had evidence of cystitis. Hematuria has occasionally been noted in amyloidosis. Knowledge of the pathogenesis of this symptom is limited but its origin from the renal parenchyma has been postulated.[11] It is noteworthy that hematuria did not occur in these cases except as a complication of renal vein thrombosis.

In investigations of renal function the blood urea nitrogen levels varied from 7 to 80 mg. % at the time of diagnosis, with a mean of 27 mg. %; the upper limit of normal is less than 20 mg. %. Using the endogenous creatinine clearance as a measure of the glomerular filtration rate, of the eight patients studied, six had a reduced clearance, the mean reduction being 34% below normal. Apart from the complication of renal vein thrombosis which may lead to a rapid deterioration in renal function, other factors which might have influenced the progression of renal dysfunction have not been identified.

By electrophoresis of the serum proteins, the albumin was low and the alpha$_2$ globulin was elevated in nine of the 10 cases studied; in six of these the albumin showed a reduction greater than 50% below the lower limit of normal. The serum cholesterol was elevated in 10 cases; and this elevation was roughly proportional to the fall in serum albumin. These patients presented with proteinuria and this was usually the most prominent finding during the development of the nephrotic syndrome. Apart from clear-cut evidence of renal disease, there was usually no overt evidence of organ involvement elsewhere except for the three patients with enlargement of the liver. No clinical difference was apparent between those with primary and those with the secondary form of amyloid disease. In the latter, proteinuria occurred during the course of the initiating illness, and as time went on the nephrotic syndrome became the prominent feature in the patient's disease.

Diagnosis of amyloidosis under these circumstances requires a high index of suspicion. The Congo Red test was employed in nine cases and the percentage of dye remaining in the blood at one hour is shown in Fig. 1. The shaded area represents the normal range in which up to 60% of the dye is left in the blood at one hour. Using these criteria, only one patient had a normal test, the remainder showing increased removal of dye from the blood. It must be emphasized, however, that the Congo Red test is of dubious value in establishing the diagnosis of amyloidosis. Not only are there false positive and false negative tests but the criteria which render a test positive or negative are in dispute.[12] Depending on the technique of determining the dye concentration in the blood and also on the method of calculation, the results of the test may vary considerably.[13] In addition to these difficulties, amyloid material varies markedly in its affinity for the dye in both experimental animals and human patients. Finally, there are many factors which affect the removal of Congo Red dye from the blood.

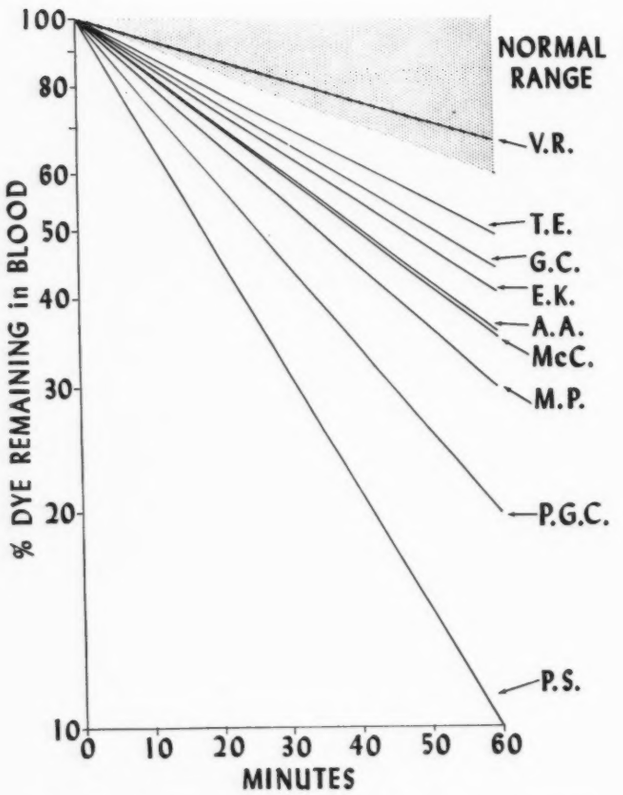

Fig. 1.—The results of the Congo Red test in nine cases.

Of the six cases with primary amyloidosis the correct diagnosis was suspected in three. However, two of these patients were sisters, one of whom had a thyroid nodule removed before being seen by us. This nodule was known to contain amyloid material and was a clue to the correct clinical diagnosis in these two cases. In the other case the patient presented with acute ulcerative colitis and a nephrotic syndrome. A diagnosis of secondary amyloidosis was made but at autopsy the disease was primary; the colitis was due to amyloid involvement of the bowel.

The tissue diagnosis from biopsy specimens was relatively easy except for one case (Case 7) in which the initial diagnosis was glomerulonephritis. Seven months later this patient presented with an

enlarged liver, and biopsy showed the presence of amyloidosis. On review of the biopsy specimen from the kidney the presence of amyloid was noted. In the six patients with secondary amyloidosis the diagnosis was suspected in all. It was established by needle biopsy in three cases, by surgical biopsy in one case and by autopsy in three cases. Three of this group are still living, and recent investigation showed relatively normal renal function in all. The blood urea nitrogen levels range from 10 to 16 mg. %, the endogenous creatinine clearances from 83 to 110 ml./min., and the maximum specific gravity measurements from 1.023 to 1.029.

Fig. 2.—Thrombi in the renal veins in Case 9.

Gross autopsy findings in the eight patients who have died showed that the most significant abnormality was bilateral renal vein thrombosis, which was present in two primary cases and one secondary case. A review of the literature by Barclay, Cameron and Loughridge in 1960 reported only 39 cases with this complication of renal amyloidosis; these authors added nine cases of their own. Only one case of renal vein thrombosis associated with primary amyloidosis is included in this review. The clinical course following renal vein thrombosis from any cause may include the development of the nephrotic syndrome or a sudden deterioration in renal function with oliguria and uremia.[2, 14] Although the onset of the renal vein thrombosis cannot be determined accurately in our cases, all the patients are thought to have died within one month of its development. The sudden onset of oliguria with increasing uremia was present in each case. One patient (Case 6) probably developed this complication postoperatively, one (Case 9) while on intensive diuretic therapy (see Fig. 2), and the third (Case 11) when he was bedridden. The factors which are important in the pathogenesis of this complication have been discussed[14] and it is reasonable to conclude that the clinical status of the patients developing this complication predisposed to venous thrombosis.

Microscopic examination demonstrated the involvement of the kidney, spleen and adrenal in all patients who died; the liver was involved in four cases of primary amyloidosis but in three of these the infiltration was confined to the blood vessels. Similar involvement was noted in two cases with secondary amyloidosis and in one of these the infiltration was confined to the blood vessels. In general, the disease was more widespread in primary amyloidosis but the distribution did not permit a separation of the primary from the secondary form. The staining characteristics of the amyloid tissue have not been studied in detail in all cases autopsied. However, it is clear that in the individual case, variations in the staining characteristics do not permit a distinction between the primary and secondary form.

Little can be said about treatment of amyloidosis; the initiating cause should be eradicated wherever possible. The relationship of corticosteroid therapy to the progression or regression of amyloidosis is equivocal.[6] Whereas resorption of amyloid has been demonstrated experimentally, little is known about this in humans. Particularly relevant is the emphasis by Parkins and Bywaters[15] that regression of the enlarged liver and spleen, disappearance of proteinuria, reversal of the Congo Red test and return to normal of the serum protein electrophoretic pattern are insufficient criteria upon which to conclude that all of the amyloid has disappeared.

SUMMARY

Twelve cases of amyloidosis, six primary and six secondary, have been described. The clinical and laboratory findings which suggest the diagnosis have been discussed in some detail.

Particularly noteworthy in this study is the development of renal vein thrombosis in three patients.

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CLINICAL EXPERIENCE WITH CYCLOPHOSPHAMIDE IN MALIGNANT DISEASE*

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WITH AN awareness of the temporary and often incomplete palliation afforded by nitrogen mustard and other well-known alkylating agents to patients suffering from malignant disease, from mid 1959 the newer nitrogen mustard derivative, cyclophosphamide, was used in selected cases. By October 1960, 67 patients, most of whom had advanced malignant disease, had been treated, and have since been followed up for a minimum period of six months.

The selection of patients was based on the clinical decision that an alkylating agent might be of benefit to the patient, and that further surgery or radiation if used alone would be less effective. The literature indicated that cyclophosphamide is less toxic than nitrogen mustard, and it seemed reasonable to try this drug in a number of cases in combination with radiation therapy to determine if there was any additive effect. It was agreed, when the study was begun, that if toxicity was high, or if the patient seemed to deteriorate rapidly, the drug would be withdrawn.

Review of the Literature

Table I summarizes the results of published series in which definite figures for response and failure are recorded. Sometimes the figures quoted are difficult to interpret, and the reported result is classed as a "response" if the authors considered the drug useful. This obviously detracts from the value of the table but it does give a general picture of the numbers and types of cases that have been reported to date. The numbers of cases in each category are limited, and details of the pathological findings often are not described, so that the data regarding the response to the drug are not to be accepted uncritically.

At the present time there is a great need for some generally accepted scheme by which the response to an anticancer drug can be recorded. This subject is extremely complex, and it seems probable that separate criteria will be necessary for the evaluation of different types of neoplasms. The natural history of each is of the utmost importance and must be given due attention in the formulation of such criteria. This is particularly important in the lymphomas and leukemias, but this factor is less of a problem with the group of solid tumours.

Most authors list their own criteria, but these vary widely. For example, one author cites as "good response" complete objective and subjective remission for six months, while at the other extreme some workers consider objective remission to have occurred if any one physical sign diminishes. Another considers that a case cannot be evaluated unless there is some definite pathology which can be measured. These views are widely divergent and the application of them does not always give a clear indication of the usefulness of the drug.

In addition to the results quoted in the table, a single excellent result in a patient with chorionepithelioma is reported by Eufinger.[29] Simon[34] reports a series of patients with glioblastomas with 50% favourable results following treatment with cyclophosphamide, but in our opinion these were not followed up for an adequate period. Delmon[28] claims useful and objective responses in patients with carcinoma of the stomach, in contrast to the experience of other authors.

A survey of the dosage used by various authors shows wide variation both in the amount of drug given and the duration of treatment. For example, Coggins, Ravdin and Eisman[5, 27] administer the drug in one of two schedules: in the first regimen a single large intravenous dose, varying from 45 to 100 mg. per kg. of body weight, is given, with repetition of this same dose, or three-quarters of it, in about three weeks if the patient's general condition and blood counts permit. The other regimen used by these workers consists of high dosage repeated daily for six days, most patients receiving an average daily dose of 7.5 mg./kg. Several of these courses are given, depending on the tolerance of the patient and his blood-forming tissues. There is some indication that a higher proportion of responses occurs with these high-dose schedules than in other series. Other regimens reported consist of once-weekly or twice-weekly medication with a wide variation of dosages. However, in most of the series reported, the authors favour prolonged therapy, giving daily doses of approximately 3-4 mg./kg. The drug is usually stopped in the event of improvement, remission or toxicity, or when a predetermined cumulative dose has been reached. When a response is obtained, some workers prefer to continue with maintenance treatment at daily or weekly intervals, usually at a reduced dosage; on such maintenance therapy some extraordinarily high total doses have been given over long periods of time.

Administration and Dosage

Because many of our patients could attend on an outpatient basis, a prolonged course was given at moderate dose level; treatment was started with an intravenous injection of 100 mg. of cyclophosphamide, followed by 200 mg. daily, irrespective of height and weight; this was equivalent to 3 to 4

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TABLE I.

Disease	*Numbers responding over No. of cases treated*	*Total*	*% response*	*References*
RETICULOSES				
Hodgkin's disease	1/2 3/6 15/26 5/6 2/3 4/4 1/1 9/14			1, 2, 3, 6, 7, 11, 12, 12A
	10/14 7/12 14/15 16/17 3/3 2/2 3/4 6/11 1/1	102/141	72%	14, 16, 17, 18, 19, 21, 23, 24, 26
Reticulum cell sarcoma	1/1 4/4 3/5 1/2 0/1 1/1 2/2 1/1			1, 2, 3, 6, 11, 12, 12A, 14,
	1/1 1/1 3/3 1/1 5/5 0/1 2/6	26/35	74%	15, 18, 19, 21, 22, 23, 24
Giant follicular lymphoblastoma	0/1 2/2 1/1	3/4	—	2, 12, 18
Lymphosarcoma	3/4 6/14 4/7 1/2 2/5 5/5 1/1 2/3			2, 3, 6, 7, 8, 11, 12, 12A
	1/1 2/2 2/3 7/7 1/1 4/6 3/6	44/67	66%	16, 17, 18, 19, 21, 23, 24
Malignant lymphoma (unspecified)	9/13 5/7 1/1 1/2	16/23	70%	5, 10, 14, 24
Chronic lymphatic leukemia	8/19 2/2 5/6 6/6 2/4 4/5 1/1 1/5 0/1	29/49	59%	3, 11, 12, 12A, 16, 18, 21, 24, 25
Chronic myeloid leukemia	1/1 9/9 4/4 0/1 0/2	14/17	82%	6, 11, 12, 12A, 24
Subacute eosinophilic leukemia	0/1	0/1	—	16
Acute leukemia	1/10 4/14 0/1 2/2 6 (C)/13 13(C)/37 9 (A)/45 1/1 0/5 5/9	41/137	30%	2, 3, 5, 7, 9, 13, 13, 19, 21, 15
	C—children, A—adults, remainder unspecified			
Polycythemia rubra vera	1/1 1/1	2/2	—	12, 18
Multiple myeloma	1/1 0/1 0/13 3/5 0/5 1/1 1/1 3/4 9/14 2/2 0/3	20/50	40%	1, 2, 3, 6, 10, 11, 12A, 16, 18, 21, 24
Mycosis fungoides	1/1 0/1	1/2	—	2, 16
CARCINOMAS				
Tongue	0/4	0/4	—	24
Parotid	1/1	1/1	—	6
Larynx	1/1 2/2 0/5	3/8	—	5, 10, 24
Nasopharynx (epidermoid)	2/2	2/2	—	10
Tonsil	1/1	1/1	—	1
Lymphoepithelioma	1/1 1/3 1/1	3/5	—	2, 24, 26
Pharynx and larynx	1/4 0/9	1/13	8%	2, 6
Thyroid	0/1 0/2	0/3	—	5, 24
Trachea	0/1	0/1	—	1
Lung	10/16 1/6 3/6 2/9 2/5 3/4 0/1 0/1 0/3 3/30 0/1	24/82	29%	1, 2, 3, 5, 6, 10, 16, 18, 19, 24, 26
Esophagus	0/1 0/4 0/1	0/6	—	6, 24, 26
Stomach	1/3 0/1 0/1 0/5 0/5	1/15	7%	1, 3, 19, 24, 25
Colon	0/1 0/1	0/2	—	1, 19

TABLE I.—*Continued*

Disease	*Numbers responding over No. of cases treated*	*Total*	*% response*	*References*
Carcinoid tumour	0/1	0/1	—	24
Rectum	0/1	0/1	—	18
Anus	1/2	1/2	—	10
"G.I. tract"	0/11 2/16	2/27	7%	2, 5
Pancreas	0/1 0/1	0/2	—	2, 3
Hepatoma	0/1 0/1	0/2	—	24, 26
Adrenal	0/1 0/1	0/2	—	6, 19
Kidney carcinoma	0/1 1/2 0/1 0/1 0/6	1/11	9%	1, 2, 5, 19, 24
Wilms' tumour	0/1 0/2 0/1	0/4	—	19, 20, 24
Renal pelvis	1/1	1/1	—	26
Bladder	0/2	0/2	—	24
Prostate	0/1 0/1 2/8	2/10	20%	5, 19, 24
Testis (embryonal)	1/2 1/1	2/3	—	16, 19
(Unspecified)	0/2 0/1	0/3	—	2, 5
Ovary	2/3 2/5 0/2 6/9 1/1 1/1 3/4 8/23 1/2	24/50	48%	1, 2, 3, 5, 6, 10, 19, 24, 25
Fallopian tube	0/1	0/1	—	6
Corpus uteri	1/2 1/5 2/8	4/15	27%	2, 5, 24
Cervix uteri	1/1 1/9 1/3 1/3 5/28 1/1	10/45	22%	1, 2, 5, 6, 24, 26
Vulva	0/1	0/1	—	24
Breast	2/5 0/6 1/1 3/8 1/1 2/13 0/4	9/38	24%	1, 2, 3, 5, 14, 24, 26
Male breast	0/1	0/1	—	5
Skin	0/1	0/1	—	26
Sweat gland	0/1	0/1	—	24
Melanoma	0/1 3/8 1/2 0/1 1/3 0/3 1/2 0/1 1/5 1/1	8/27	30%	2, 5, 10, 11, 12, 14, 16, 19, 24, 25
Carcinomatosis (primary unknown)	1/3 2/4 1/3 4/9 0/2 0/2 0/5 2/2	10/30	33%	1, 2, 5, 11, 19, 21, 24, 26
Effusions	2/5 3/7	5/12	42%	4, 24
SARCOMAS				
Osteogenic sarcoma	1/3 0/1	1/4	—	20, 24
Ewing's tumour	1/1 0/1 1/1	2/3	—	16, 20, 25
Fibrosarcoma	1/2	1/2	—	2

TABLE I.—*Concluded*

Disease	*Numbers responding over No. of cases treated*	*Total*	*% response*	*References*
Liposarcoma	0/1 1/1	1/2	—	2, 18
Myxosarcoma	0/1	0/1	—	25
Rhabdomyosarcoma	1/2 1/1 0/1 3/4 (children)	5/8	—	2, 7, 16, 20
Leiomyosarcoma	0/3	0/3	—	24
Synovioma	0/1	0/1	—	24
Sarcoma (undifferentiated)	0/1 0/1 0/1 0/1	0/4	—	2, 16, 24, 26
Neurofibrosarcoma	0/1	0/1	—	5
Schwannoma	0/1	0/1	—	16
Kaposi's sarcoma	0/1	0/1	—	24
MISCELLANEOUS				
Mesothelioma	0/2	0/2	—	24
Pleura, unspecified	1/2	1/2	—	1
Teratoma	1/2 0/1	1/3	—	20, 24
Neuroblastoma	0/3 1/1	1/4	—	20, 25
Ependymoma	0/1	0/1	—	24

mg./kg. In a few patients the dose was cautiously raised to 400 mg. daily, but nausea was more troublesome at this level and in a number of cases the dose had to be reduced again.

At first the treatment was given for five days each week but it was soon recognized that this rate of administration, 1 g. weekly, was too low and time-consuming. Later, treatment was given six or seven days each week directed toward the administration of a minimum of 5 g. of cyclophosphamide in four weeks wherever possible, and continuing to higher dosage if this was well tolerated and a response to the drug was obtained. After one to three weeks of intravenous injections many patients, particularly those who went home, continued with oral cyclophosphamide at the dosage of 200 mg. daily (4 x 50 mg. tablets).

During and after treatment, all patients were examined frequently, blood counts were done, and where possible the size of tumour masses was measured and serial radiographs were taken.

Side Effects

From the patient's point of view the only important side effects are nausea and alopecia. The clinician's main concern is depression of the bone marrow. Other side effects occur, but they are infrequent and depend largely on the dosage used.

Some nausea occurred in 60% of our patients and was often evident within the first week of treatment. In almost every instance its severity could be lessened with the commonly used antiemetic drugs. Vomiting occurred at some time in 22% of patients. Other gastrointestinal effects were uncommon: two patients had diarrhea; one had hematemesis from a gastric ulcer which may be considered coincidental; and four patients complained of a foul taste in the mouth after intravenous administration of the drug, coming on a few minutes after the injection and lasting for several hours.

The extent of the disease bears a relationship to the incidence of nausea and vomiting; those patients with localized disease, who were in fairly good health, usually took the drug well with little upset.

Alopecia of some degree occurred in nine of 42 men (21%) and in nine of 25 women (36%). The incidence in men is higher than was expected and may be due to the fact that leading questions were asked concerning this complication. The total dosage is important: if patients who received less than 3 g. are excluded, the overall rate of alopecia in men and women combined rises to 36%. Hair loss, usually evident as an excessive accumulation on the comb, was noticed some two to three weeks after the drug had been started. Hair loss usually

persisted during the period of administration and for a short time thereafter; pubic and axillary hair was unaffected.

Hair often began to grow again during the period of oral maintenance therapy. Complete alopecia occurred in only four cases. Most of our patients suffered a diffuse thinning of scalp hair; patchy hair loss was rather uncommon, although it has been reported in 50% of one reported series. Regrowth was usually complete in three months, at least as far as hair thickness was concerned, and most patients were satisfied with their new head of hair. In one woman with straight greying hair, regrowth of darker and more curly hair occurred, to her pleasure.

No other alkylating agent currently in use produces alopecia. From a survey of the literature the occurrence of alopecia seems related to the total dosage and the time over which cyclophosphamide is administered. Coggins, Ravdin and Eisman,[5, 27] workers who employed the highest dosage schedule, reported an alopecia rate of 90% which was equally distributed between the sexes. Bergsagel and Levin[2] report that 27% of their patients had hair loss. Foye *et al.*[10, 10a] noted patchy alopecia in six of 25 patients (25%), and Matthias, Misiewicz and Bodley Scott[18] give evidence of alopecia in six in 45 cases (13%). Papac *et al.*[19] describe 10 patients in 31 (32%) who are equally divided between those with patchy and those with diffuse hair loss. Haar *et al.*[12] record five in 20 (25%), and Shnider *et al.*[24] 15 in 47 (32%) of those treated by oral administration on various regimens and an incidence of 19% of those treated by intravenous injection. Hoogstraten *et al.*[13] report that 15% of patients receiving over 4 g. had this complication. Regrowth of hair seems to be the rule.

In four patients throbbing headaches were a prominent symptom; these subsided when the drug was discontinued. A sense of tiredness was a common symptom but was seldom volunteered by the patient. It is hard to dissociate this symptom from the weariness that the underlying disease may cause.

Three patients developed herpes zoster: one patient had lymphosarcoma, the other two had Hodgkin's disease. In both cases of Hodgkin's disease the herpes was extensive, but need not be ascribed to cyclophosphamide because it occurs frequently in the natural evolution of this disease.

When radiotherapy was combined with drug treatment there may have been a slight increase in nausea and gastrointestinal disturbances, but in no case was this symptom excessive. These two methods of treatment can be combined conveniently.

Thrombophlebitis at the site of injection did not occur; it was usually possible to complete the whole course of intravenous injections through one vein.

Those authors who employ a high dosage in a short time have recorded such side effects as dizziness, blurring of vision and sterile chemical cystitis. These symptoms were not observed in our cases or in other series where a prolonged period of treatment was used. Haas[30] has reported disturbance of wound healing when cyclophosphamide was given at the time of laryngectomy. This is a nonspecific complication which has been reported with the use of other alkylating agents in association with major surgery.

The effect of this agent on the hematopoietic system is described in detail in other reports, especially those of Petrides and Moncke[32, 33] and Nissen-Meyer and Hoest.[31] This aspect of the subject will not be dealt with here. Most of our patients had previous chemical or radiation therapy, which complicated the hematological picture.

Of all the patients treated, the white blood count fell to less than 2000 per c.mm. in 19 cases. These findings confirm the work of others who found that cyclophosphamide depresses the platelet count much less than nitrogen mustard and other alkylating agents. The platelet count fell to below 100,000 per c.mm. in only three cases; and the count returned to normal levels rapidly when the drug was discontinued.

Cyclophosphamide is the safest alkylating agent available at the present time. The white blood cell count can be reduced to 1250 without danger, provided the platelets do not fall significantly below 100,000 per c.mm. The degree of white cell and platelet depression is related to the extent of bone marrow involvement, liver disease[2] and previous chemical or radiation treatment.

RESULTS

Table II shows the response in 67 patients with advanced malignant disease treated with cyclophosphamide at the Edmonton Cancer Clinic. Histological proof of diagnosis was not obtained in one patient; and no patient was lost to follow-up. A "good result" implies relief of the principal symptoms and regression, or at least arrest, of previously progressing lesions, for a period as long as that which occurs with present methods of treatment. Several favourable responses are classified as "partial response", where new lesions appeared either during or after treatment although regression of the main mass or masses was observed. Minor degrees of improvement have been ignored.

Hodgkin's Disease

Seven patients with generalized Hodgkin's disease were treated, three males and four females. Six had been diagnosed at least three years previously and had multiple treatments either by radiation or alkylating agents in the past. This reference

TABLE II.

				Evaluation of response							
Disease	*Sex*	*Age*	*Total dose (G.)*	*Good*	*Partial*	*Uncertain*	*No effect*	*Inadequate dose*	*Survival (weeks)*	*Living or dead on April 1/61*	*Remarks*
Hodgkin's Disease	M	56	1.2					1	2	D	Total duration of disease—18 months. Moribund when treated.
	M	27	4.7				1		13	D	Total duration of disease—4 years.
	M	55	5.0		1				24	D	Prior and concurrent ACTH. Total duration—4 yrs.
	F	41	2.0		1				45	D	Subjecti e improvement. Total duration—5 years.
	F	15	1.3	1					58	L	Previous duration 3 years with many treatments. Seemed terminal when cyclophosphamide started.
	F	18	1.8+R	+					58	L	Previous history—3 years.
	F	35	2.3		1				78	L	New nodes developed during treatment, but general condition greatly improved—previous duration—5 years.
7 cases				2	3	0	1	1		3L	
Lymphosarcoma	M	27	5.0		1				20	D	Axillary nodes resolved dramatically but disease progressed generally.
	M	80	0.7+R					1	33	L	Good response to radiation.
	M	54	2.7+R					1	10	D	Total duration 5 years with repeated radiation. Far advanced when treated with cyclophosphamide.
3 cases				0	1	0	0	2		1L	
Reticulum cell sarcoma	F	62	2.7+R					1	6	D	Primary probably stomach. Radiosensitive, but recurred rapidly.
	F	57	6.1				1		15	D	?Primary in sternum. Radiosensitive. New lesions developed during treatment with cyclophosphamide.
	M	41	8.0		1				26	D	Primary ischiorectal fossa 8 years previously. On cyclophosphamide some lesions regressed, others advanced.
	M	56	9.4		1				14	D	Good remission on I.V. cyclophosphamide and cortisone, but relapsed on oral cyclophosphamide.
4 cases				0	2	0	1	1		0L	
Multiple myeloma	F	46	8.3	1					53	L	Good subjective response. Lesions stationary radiologically.
	M	57	9.0	1					37	D	Recalcification of bone lesions. Rapid terminal deterioration with liver enlargement (amyloid).
	M	88	7.0+R Oral	+					32	D	Striking result. Almost moribund at start.
	M	71	15.7	1					77	L	Pain relieved. Lesions stationary.
	M	61	6.0				1		24	D	Downhill course unaffected by cyclophosphamide and by urethane.
	F	38	5.7+R	1					59	L	5-month remission including unirradiated areas.
	M	59	2.9+R					1	17	D	Hemiplegic. No improvement.
7 cases				5	0	0	1	1		3L	
Ewing's sarcoma	M	14	10.8+R	1					44	D	Widespread metastases, four courses of treatment.
	M	9	2.5+R			1			29	L	Primary treated (femur) with full radiation. Impossible to assess effect of cyclophosphamide.
Fibrosarcoma	M	66	2.9					1	15	D	Primary quadriceps. Continued growth of lung metastases.
	M	19	4.7				1		23	D	Primary biceps. Lung metastases.
Leiomyosarcoma	F	48	3.8+R				1		18	D	Primary probably ovary. Advanced.
	F	53	4.8				1		20	D	Primary stomach. Radioresistant.
Sarcoma (undifferentiated)	M	12	6.7		1				16	D	Regression of primary. No change in lung metastases.
Lymphoepithelioma of pharynx	M	68	5.2+R				1		26	D	Chinese. Temporary response to radiation.
	M	37	5.5				1		28	D	Total duration 3 years with radiation. New lesions developed during treatment.
Tongue	M	71	2.3				1		8	D	Very advanced, squamous cell grade III.
Adenocarcinoma of stomach	M	56	7.5 (Oral)				1		13	D	Widespread secondaries.
	M	72	7.1+R			+			38	L	Good result in conjunction with radiation 3500 rad.
	M	60	5.2+R				1		9	D	Liver metastases.
3 cases				0	0	1	2	0		1L	
Adenocarcinoma of large bowel	F	33	1.6					1	9	D	Carcinomatosis peritonei.
	M	73	2.1+R			+			26	D	Cecum. Probably better palliation than radiation alone.
	M	50	11.0+R			+			53	L	Cecum. 3 separate courses. Probable growth restraint.
	F	65	4.5+R			+			38	L	Colon. Probably better than radiation alone.
4 cases				0	0	3	0	1		2L	
Anaplastic carcinomatosis of the omentum	F	59	6.0			1			14	D	Subjective improvement.
Ovary	F	46	7.7	1					57	L	Abdominal carcinomatosis, undifferentiated. Subsequent radiation to pelvis only.
	F	44	3.6+R			+			34	L	Extensive serous cystadenocarcinoma. 3600 rad; impossible to assess separately. Excellent response.
	F	34	6.0				1		21	D	Papillary cystadenocarcinoma.
	F	62	1.1+R					1	13	D	Treatment poorly tolerated.
4 cases				1	0	1	1	1		2L	

TABLE II.—*Continued*

				Evaluation of response							
Disease	*Sex*	*Age*	*Total dose (G.)*	*Good*	*Partial*	*Uncertain*	*No effect*	*Inadequate dose*	*Survival (weeks)*	*Living or dead on April 1/61*	*Remarks*
Testis (embryonal cell carcinoma)	M	49	4.3+R				1		16	D	Radioresistant.
	M	38	6.1+R				1		22	D	Slight response to radiation.
	M	23	1.2+R					1	11	D	Radioresistant.
	M	32	5.8				1		6	D	Previous good response to radiation, very sensitive.
4 cases				0	0	0	3	1		0L	
Hypernephroma	M	40	3.7+R				1		27	D	Bone and lung metastases progressed.
	F	63	3.5+R		+				33	L	Response to combination; previously radioresistant. Lung metastases unaffected.
	F	50	8.0+R		+				15	D	Subcutaneous metastases responded better to combination than to either agent separately.
	M	74	5.9+R	+					23	D	Very large masses responded. Radiation 4400 rad in 8 weeks.
	F	78	2.6+R					1	14	D	Radiation dose small.
	F	64	3.1+R				1		19	D	Primary responded to 3500 rad, but lung metastases appeared.
6 cases				1	2	0	2	1		1L	
Bladder	F	36	5.0				1		34	L	Lung metastases progressed.
Cervix uteri	F	45	3.0				1		17	D	Radioresistant, stage III.
Corpus uteri	F	35	4.5+R			+			23	D	Growth restraint in conjunction with radiation and progesterone.
Carcinoma of lung	M	64	7.6+R			+			12	D	Excellent regression but died of mycotic pneumonia. Squamous.
	M	60	8.5				1		15	D	Anaplastic; radiosensitive.
	M	50	13.5		1				21	D	Dramatic resolution of skin nodules, but other lesions progressed. Anaplastic.
	M	47	4.2				1		9	D	Oat cell. Skin nodules and liver metastases.
	M	44	2.1					1	26	D	Epidermoid. Treatment interrupted by hematemesis.
	M	67	3.0+R				1		4	D	Epidermoid. Rapid decline.
	M	70	1.0					1	11	D	Epidermoid.
	M	71	12.0				1		24	D	Epidermoid. Lesions progressed.
	F	57	4.8	1					13	D	Epidermoid. Cerebral metastases. Seven weeks' remission.
9 cases				1	1	1	4	2		0L	
Mesothelioma of pleura	M	50	0.6					1	2	D	Moribund.
Skin	M	75	4.0				1		14	D	Inguinal nodes secondary to buttock.

TOTAL
67 cases (30 with radiation) "Good" 11; "Partial" 11; "Uncertain" 9; "No effect" 23; "Inadequate dose" 13; 15 "Living"

EXPLANATORY NOTES:

1. In the column headed "Total Dose," the symbol "+R" is added when radiation therapy was given concurrently. Small fields to local deposits irrelevant to the general course of the disease have been ignored in a few instances.
2. In "Evaluation of Response" the symbol "+" indicates a favourable response in conjunction with radiation. These are only entered as "good" or "partial" if this was definitely better than could be expected by the radiation dose given. Otherwise such cases are entered as "uncertain" since the benefit could not definitely be ascribed to the drug.
3. A total dose of cyclophosphamide less than 3.0 g. is entered as "inadequate dose" unless there was a favourable response.
4. We have ignored minor degrees of subjective improvement or very temporary response.
5. The minimum follow-up period is 6 months.

to the natural history of the disease is important because patients who survived for this length of time must be those with the less malignant variants of the disease. One male, almost moribund when treatment was started, died two weeks later; another, who was first diagnosed four years previously, showed no worthwhile response; our third male patient received little benefit except for slight symptomatic improvement and reduction in fever.

The female patients had a much better response; three out of four are still alive and in moderately good health. The patient who died had extensive disease accompanied by persistent pruritus which had made her life miserable for three years; this symptom was relieved considerably by treatment with cyclophosphamide. The three patients who are living have had remissions lasting longer than one year. All had concurrent radiotherapy to mediastinal masses. Regression occurred in one patient who previously had received radiation to the mediastinum with little evidence of response. Each of these patients has since received an occasional single treatment with x-ray to painful areas, but this cannot account for their general return of well-being; one patient previously bedridden is now able to walk.

The results reported in the literature are encouraging. Although it is not possible to separate with certainty subjective and objective responses, in a fairly representative group 55 of 92 cases (60%) showed objective response and worthwhile effect. If subjective criteria are included, a much higher

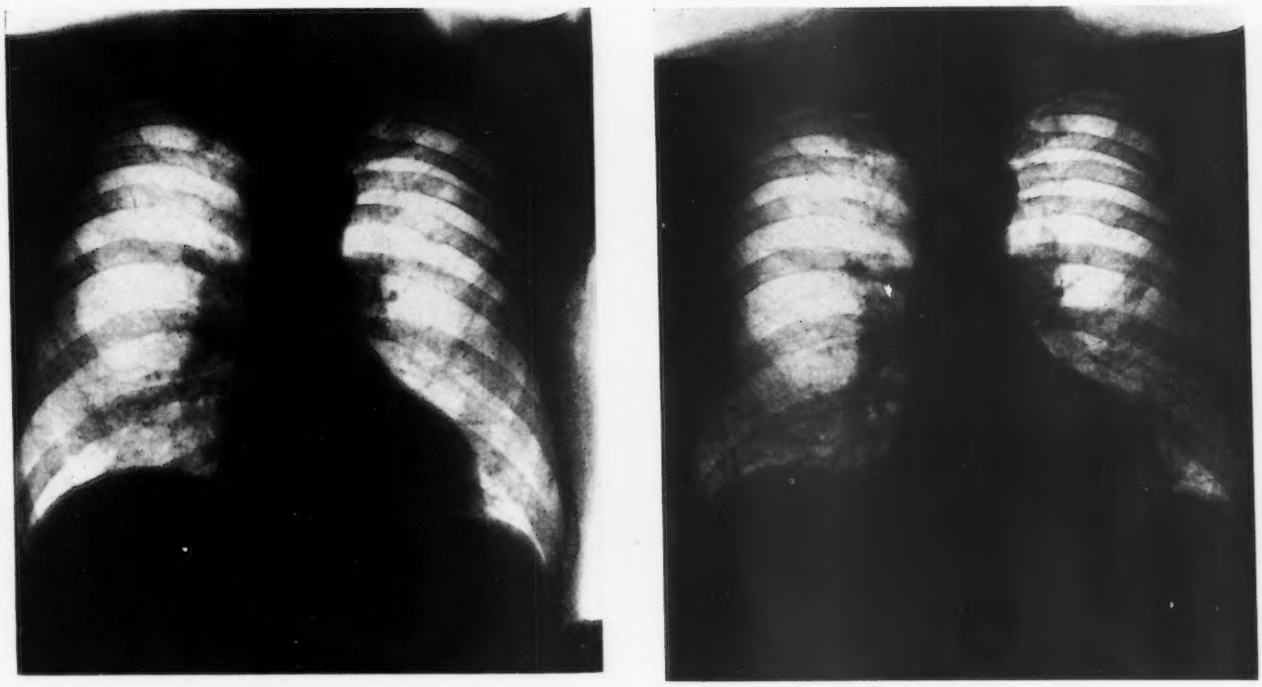

Fig. 1a

Fig. 1b

Fig. 1a.—Multiple myeloma. Male aged 57. Chest radiographs of December 14, 1959, before treatment. **Fig. 1b.**—February 24, 1960, after treatment with cyclophosphamide. Note particularly recalcification of lesions in right 5th rib and left 7th rib.

percentage of patients obtain benefit. Matthias, Misiewicz and Scott[18] report a favourable objective response in 65% and subjective improvement in 88%.

Lymphosarcoma

There were three cases of lymphosarcoma in this series. One elderly patient had received an inadequate dosage, but as he showed an excellent response to radiation, cyclophosphamide was discontinued. The second patient had extensive disease which was completely unaffected by the drug. The third had widespread disease but had reduction in the size of enlarged axillary lymph nodes although the disease as a whole progressed. The literature records a satisfactory objective response in about 55% of 36 collected cases of lymphosarcoma. The duration of remission is usually not given.

Reticulum Cell Sarcoma

Four patients with this disease were treated, but no worthwhile result was obtained. This disease pursues a most varied natural history. Localized tumour masses can often be controlled by radiation, but in our experience generalized involvement is rarely amenable to chemotherapy, and radiaion therapy in such cases produces little more than transient palliation.

The details of the cases of reticulum cell sarcoma treated are listed in Table II. Two patients receiving 8.0 and 9.4 g. respectively had slight improvement but the treatment was of little real value.

A survey of published cases showed that favourable response was described in 74%; details of the extent of the disease and the duration of the therapeutic result were generally not stated.

Multiple Myeloma

Seven patients with multiple myeloma were treated, and in most of these cyclophosphamide was the first anticancer drug to be given. One patient had a prolonged course of urethane previously without effect.

Five of the seven patients are classified as having "good" results. All of these had marked symptomatic improvement and although they had concurrent radiation therapy to certain areas, relief of pain was also observed in unirradiated areas. Three of these patients are living one year or more from the beginning of treatment; they have not had any evidence of relapse. Two of the "good" cases died, at 31 and 36 weeks respectively, one at age 89. Both of these patients died of the disease, but had had a definite remission which was ascribed mainly to cyclophosphamide.

In three of the patients with "good" response, prednisone in doses up to 15 mg. per day was given to maintain the white blood count. This was stopped as soon as the leukocyte count was satisfactory; discontinuing prednisone did not seem to result in early relapse. One patient had definite radiological evidence of recalcification of a number of lesions in ribs and elsewhere. This is illustrated in Fig. 1.

The results reported in the literature are not quite so encouraging as these, although the overall

response rate of 40% is impressive in a disease for which no satisfactory systemic therapy is known. A few treated cases in the literature have shown changes towards normal in the electrophoretic pattern,[16, 32] but most workers rely on the patient's subjective response. Spontaneous reduction in pain and a temporary arrest of the disease occasionally occurs and may be difficult to distinguish from the effects of therapy.

A series of 13 cases in whom no detectable response was obtained[3] were treated with oral cyclophosphamide only. The only other series of comparable size (Matthias, Misiewicz and Scott) showed nine patients responding out of 14 treated with intravenous injections of the drug. These authors reported a higher incidence of leukopenia during the treatment of this disease with cyclophosphamide than in other reticuloses so treated; this is in line with our experience.

Ewing's Sarcoma

Two patients with Ewing's sarcoma were treated with cyclophosphamide.

The first was a boy of 14 who had an amputation above the knee for Ewing's sarcoma of the right tibia in May 1958. He was well until January 1959, when metastases in the lungs and pelvis became apparent. From then until August 1959, he had many courses of radiotherapy to bone and soft tissue metastases; there was excellent local response, including improvement in lung metastases in the one half of the chest treated. In October 1959 the boy was treated with cyclophosphamide, in conjunction with prednisone, 15 mg. daily, because he had marked marrow depression from his disease and from previous therapy. A total of 3.6 g. of cyclophosphamide was given in three weeks; marked subjective improvement occurred and there was slight reduction in the measurable lesions. Further courses of cyclophosphamide were given because of an exacerbation of symptoms: in December 1959, 1.4 g.; in January and February 1960, 3.8 g.; and in May 1960, 2.0 g. On each occasion there was subjective benefit and slight objective response of the lung lesions. Supportive treatment with local radiation and blood transfusions was also given but the main effect was definitely attributable to cyclophosphamide. This patient also had one course of nitrogen mustard without apparent benefit. He died in August 1960, 44 weeks after the first course of cyclophosphamide.

In the light of this experience, the next patient with Ewing's sarcoma was given cyclophosphamide and a full course of radiotherapy as primary treatment. The combination was well tolerated and the patient is well without recurrence seven months later.

Three similar cases are reported in the literature; two responded to treatment with this agent.

Soft Tissue Sarcoma

Five patients were treated for soft tissue sarcomas. Two had primary fibrosarcoma of the extremities, with intrathoracic metastases; in these no useful result was obtained. Two patients had leiomyosarcoma, one originating in the stomach, the other from the right ovary; again, no useful effect was observed.

The fifth patient was a boy aged 12 who had an extensive undifferentiated sarcoma of the forearm, an enlarged liver and bilateral pulmonary metastases. Treatment with cyclophosphamide had a dramatic effect; his general well-being improved greatly, and the contour of the forearm returned to normal. Despite this encouraging initial response, the size of the liver did not change and the pulmonary lesions continued to increase. Eight weeks later he began to fail and he died 16 weeks after the first treatment.

Lymphoepithelioma

Two patients with recurrent lymphoepithelioma were treated, with no appreciable result.

Cancer of Tongue

One very elderly patient with extensive carcinoma of the tongue received both cyclophosphamide and cobalt beam therapy, without benefit.

Stomach

Three patients with adenocarcinoma of stomach were treated with cyclophosphamide. The first two had widespread abdominal deposits, one with definite liver metastases; despite dosages of 7.5 and 5.7 g. respectively no worthwhile result was noted. The third patient one year after gastrectomy developed a large metastatic mass in the recto-vesical pouch with bladder invasion and hematuria. Treatment with cyclophosphamide and x-radiation gave excellent palliation; he had complete symptomatic relief for six months, after which local bleeding recurred.

Apart from Delmon's paper,[28] a survey of the literature records only one satisfactory response in 15 cases of carcinoma of the stomach.

Large Bowel

Three of our four patients with carcinoma of the large bowel were treated with cyclophosphamide in combination with local radiation; two are alive, with residual disease, at 9 and 12 months respectively. The third patient survived six months after having had good palliation. Because radiation was given only to the most prominent masses in the abdomen, we feel that the arrest of disease in the two patients still alive is largely attributable to cyclophosphamide therapy. The fourth patient did not respond, but had inadequate dosage of cyclophosphamide.

A fifth patient, not definitely diagnosed as having cancer of the large bowel but with widespread abdominal carcinomatosis, primary site unknown, is included here. He had subjective improvement with relief of pain with a dosage of 6 g. of cyclophosphamide; the remission lasted three months. Only two cases of this common disease are reported in the literature. No response followed treatment with cyclophosphamide.

Carcinoma of Ovary

Four patients with ovarian carcinoma were treated, with encouraging results. The first patient had extensive undifferentiated carcinoma with ascites, pain and vaginal bleeding. A dosage of 7.75 g. was given, with dramatic improvement in the patient's general well-being and shrinkage of tumour masses. In view of this excellent response, radiation therapy was given for the residual pelvic disease; it was tolerated well and the patient is free of symptoms more than one year later.

The second patient had a serous cystadenocarcinoma with extensive disease, extreme ascites and anemia. Large field radiotherapy was given over most of the abdomen in a tumour dose of 3600 rad in four weeks, combined with 3.6 g. of cyclophosphamide. The dose of x-radiation was high but it was well tolerated. No definite response was noted during the course of treatment. Immediately after treatment abdominal paracentesis was done on two occasions to remove accumulated ascite fluid. It has not accumulated again to date, eight months later.

The third patient, with papillary cystadenocarcinoma, showed no response to 6 g. of cyclophosphamide and died 21 weeks later. Our fourth patient had extensive disease and was not able to tolerate an adequate dosage.

The vagaries of ovarian cancer are many, and to obtain acceptable statistics in this disease a large series of patients is required. Reports of the use of cyclophosphamide in the literature show that 24 patients of 50 (48%) so treated had a satisfactory response. Cyclophosphamide should be used in the postoperative treatment of those patients in whom there is residual disease in the pelvis; the use of this drug should be combined with local radiation wherever possible.

Malignant Tumours of the Testis

Four patients with metastatic embryonal cell carcinoma of the testes were treated with cyclophosphamide, although one had inadequate dosage. All of these patients had pulmonary lesions and none of them responded. Radiotherapy had been given previously in two; one of them responded to this therapy, the other did not.

Of the six cases described in the literature two patients had a satisfactory response and both had embryonal cell carcinoma.

Hypernephroma

Six patients were treated because of hypernephroma, four females and two males. The first male patient had extensive local and pulmonary disease; he was treated with cyclophosphamide alone, without obvious effect. The second man had extensive stony-hard deposits throughout the whole abdomen. Palliative radiation therapy was given with relief of pain, and because of this response a second course of radiation was given combined with cyclophosphamide. During this second course of treatment 5.9 g. of cyclophosphamide was administered with symptomatic improvement and regression of tumour. It is difficult to be certain but there seems to have been some additive effect of the two therapeutic agents.

Our first female patient had inoperable local disease with extensive pulmonary involvement. However, the main sign was the periodic seeding of subcutaneous deposits; if these were left alone they tended to grow into large masses. Eight grams of cyclophosphamide was given over a long period, and regression of some of these masses was observed but they never disappeared completely; new masses appeared towards the end of the period of cyclophosphamide therapy. There were many subcutaneous masses of varying size; it was possible to leave some to be treated by cyclophosphamide alone, and to give additional x-ray therapy to others of comparable size. Those treated with additional radiation therapy either disappeared or absorbed to a greater extent. The pulmonary lesions were completely unaffected by the drug and even progressed.

In one of the three remaining patients some additive effect of radiation therapy and cyclophosphamide may have been evident. The tumour was locally recurrent and was previously radioresistant. Radiotherapy in the amount of 3000 rads combined with 3.5 g. of cyclophosphamide was given over a period of three weeks; the relief of pain which resulted lasted for three months.

It is hazardous to draw conclusions from six cases. Any effect obtained by radiation or cyclophosphamide was temporary, at best, but it seemed that in three of these six cases the addition of cyclophosphamide was of benefit. Hypernephroma is essentially a radioresistant lesion, especially when the volume of tumour is large. There was sufficient response in these three cases to warrant further trial of this agent in combination with radiation therapy in extensive disease. Pulmonary involvement is completely unaffected by cyclophosphamide alone.

A search of the literature is unrewarding. One case of hypernephroma out of 11 treated with this drug showed a beneficial response.

Malignant Tumours of the Bladder

One patient with cancer of the bladder, local pelvic disease and pulmonary involvement was

treated with a dose of 5 g. of cyclophosphamide, without demonstrable effect.

Carcinoma of Cervix and Corpus Uteri

One patient with squamous cancer of cervix, in an advanced stage and completely insensitive to radiation, was given 3 g. of cyclophosphamide without benefit. One patient with adenocarcinoma of the endometrium with widespread abdominal disease was treated with cyclophosphamide and 17-alpha-hydroxyprogesterone caproate (Delalutin), again with no useful result; some degree of palliation was obtained later by radiotherapy.

Lung

Nine patients with cancer of the lung and metastases were treated with this drug. All but one had had radiotherapy; four had had a thoracotomy and one a craniotomy. Histological studies showed that the tumour was an epidermoid carcinoma in six, and an anaplastic or oat cell carcinoma in three.

The therapeutic response was classified as "good" in a woman 57 years of age whose principal signs and symptoms at the time of treatment were due to intracranial metastasis from a primary epidermoid tumour of the lung. After two short-lasting responses to radiation she was treated with cyclophosphamide; in spite of the presence of liver metastases she had a remission which lasted for seven weeks before further deterioration occurred.

One patient with inoperable disease is classified in the "partial response" group because of striking and complete disappearance of ten skin nodules, one of which was proved to be carcinomatous by biopsy. However, in this patient, bone pain was not relieved and new lesions developed in the adrenals 13 weeks later, while the patient was still taking oral cyclophosphamide.

The remaining seven cases are regarded as treatment failures, with the possible exception of one patient in whom a very large epidermoid carcinoma of the lung, previously untreated, disappeared completely with cyclophosphamide in conjunction with x-ray therapy, a tumour dose of 3000 rad being given in three weeks. The patient died 12 weeks later, apparently from a mycotic pneumonia.

The results quoted in the literature show only occasional "good" responses, with the exception of the series reported by Aronovitch, Meakins and Groszman,[1] in which 10 of 15 patients with epidermoid carcinoma responded satisfactorily to cyclophosphamide, but no response was observed in one case of adenocarcinoma in this series. These authors particularly mention relief of pain due to bone metastases; we failed to obtain this result in our series with a similar dosage schedule. In the literature 24 of the 82 patients treated with cyclophosphamide showed some response, a rate of 29%.

Mesothelioma of Pleura

One patient with pleural mesothelioma was treated; he was moribund from the outset of treatment and died one week later. Two cases of this lesion are reported in the literature; a beneficial result from cyclophosphamide therapy was not observed in either of them.

Skin Cancer

One patient with enlarged inguinal nodes, secondary to squamous cancer of the skin of the buttock, was treated with cyclophosphamide without benefit.

DISCUSSION

The widely varying dosage schedules testify to the safety of cyclophosphamide. The spectrum of cytotoxic action parallels that of nitrogen mustard with some exceptions; in our view the principal useful feature of this agent is its lesser toxicity, both clinical and hematological. Remissions are as long as those obtained with the parent compound, and in some instances rather longer.

We favour intravenous medication, because most of our experience is with this route of administration and we know it to be effective. The oral route has produced good results, in our series and in others, but a study of the literature suggests that it is somewhat less effective. Intramuscular administration seems ineffective.[24] The intrapleural and intraperitoneal routes have been used, with variable results.[4, 10, 10a, 24] The use of cyclophosphamide for local perfusion is mentioned by Woodhall.[35]

We are unaware of any definite time-dose relationship in the use of this drug or other alkylating agents. This concept, important in radiation therapy, may be of equal importance in the chemotherapy of cancer. At present it seems unlikely that alkylating agents, as we know them, will ever be curative; their action is non-specific, affecting all dividing cells, normal and malignant; these agents are used with the hope that normal tissue will have greater powers of recovery, to the ultimate benefit of the host. Optimum dosage remains to be determined.

For practical purposes cyclophosphamide is less toxic to the liver parenchyma than either triethylene melamine (TEM), T.S.P.A. or nitrogen mustard. Unfortunately, metastatic disease of the liver seems to be completely unaffected by this agent; the fact that drug therapy is possible should not constitute an indication for its use in hopeless cases. However, cyclophosphamide might be tried with caution in some selected cases of sensitive reticuloses with liver involvement. Only one paper to date (Bergsagel and Levin[2]) suggests that liver damage does occur and the authors of that report cite two definite examples of hepatotoxic jaundice in a series

of 118 patients, in which cyclophosphamide might be implicated.

Metastatic disease of the lung seems particularly resistant to cyclophosphamide, even when there is evidence of an effect on lesions elsewhere. Our series included 29 patients with secondary lesions in the lung, and among these, only one response was obtained with the drug alone, the case of Ewing's sarcoma.

Cyclophosphamide has a place in the management of advanced malignant disease but new lesions may appear during treatment even in cases where definite objective evidence of tumour retrogression has occurred. The persistence of certain tumour masses while others are disappearing may be related to such factors as the blood supply or the state of the tumour bed. The appearance of new lesions in other sites during maintenance therapy, or towards the end of a definitive course of treatment, is remarkable and more difficult to understand.

We have found no mention in the literature of the possibility that this drug might disturb the overall tumour-host relationship, with progression of the disease rather than improvement. This possibility deserves critical study, but we have no evidence to suggest that it has occurred.

Indications for Cyclophosphamide Therapy

The indications for the use of this drug are not clear-cut at present, but we advocate its further trial in the following conditions:

1. *Multiple Myeloma*

To date, no effective treatment for this disease exists. Urethane is usually tried but its value is uncertain, bearing in mind the natural history of this disease. From the literature and from our studies, cyclophosphamide is of value in about 40% of cases of myeloma. Objective improvement has been indicated by a decrease in myeloma protein and return of the serum calcium to more normal levels. One of our myeloma patients showed recalcification of bone, which was a most encouraging sign.

2. *Lymphosarcoma*

Our experience with cyclophosphamide in this condition is insufficient to justify extended comment. If the response rate of 66% recorded in the literature is accepted, this agent seems to have a definite place in the management of widespread disease. In our view, radiation therapy is the treatment of choice in the early localized stage, but in those with large multiple masses a low dose of radiation therapy, combined with cyclophosphamide, should be given if practicable. Where the patient is obviously failing and anemia due to hemolysis is present, corticosteroids should be used as well.

3. *Reticulum Cell Sarcoma*

Treatment of this disease is most disappointing; no therapeutically effective drug exists but sporadic good results have been reported with all of the alkylating agents. Our survey of the literature shows the remarkably high figure of 74% of patients responding to treatment with cyclophosphamide. This figure is hard to believe, and we wonder whether some cases of lymphosarcoma and other reticuloses have been included. Nevertheless, when an alkylating agent is indicated, cyclophosphamide should be tried first.

4. *Hodgkin's Disease*

Subjective improvement occurs in 72% of patients with Hodgkin's disease and objective response in about 60%. Remissions seem to last longer than with nitrogen mustard, and perhaps longer than with chlorambucil. Cyclophosphamide may prove to be the drug of choice in treatment of this disease, despite the disadvantage of the alopecia that it so frequently causes. Radiation therapy is superior to drug treatment for localized disease, because its action is more certain and the duration of response longer.

5. *Ovarian Cancer*

Ovarian cancer is an unpredictable disease which sometimes responds to T.S.P.A. and chlorambucil (Leukeran). The literature suggests that cyclophosphamide was effective in 48% of cases of carcinoma of the ovary where this was the only agent used; therapeutic trial is indicated in inoperable or recurrent cases. Our experience suggests that this agent may be valuable in conjunction with radiotherapy in this condition.

Since October 1960 we have had the opportunity of treating another four patients with ovarian cancer with combined cyclophosphamide and radiation therapy, and the results in three of these patients have been very encouraging.

6. *Acute Leukemia*

From the literature, a response to cyclophosphamide was noted in 41 of 137 patients with acute leukemia (30%). This does not imply remission, which seems to occur in about 11 to 15% of adults and children with acute lymphatic leukemia, when they are treated with cyclophosphamide after other drugs have ceased to be effective. Weekly therapy may be more effective than daily treatment.[13] Admittedly this rate is low and the remissions have not been of long standing, but we feel it is worthwhile keeping this drug in mind for possible use in these circumstances.

7. *Combination with Radiation Therapy*

The addition of cyclophosphamide to radiotherapy has already been mentioned for treatment

of patients with advanced ovarian and other cancers. We suggest that its use be investigated in selected cases of tumours which are not usually amenable to radiotherapy, particularly adenocarcinoma of the large bowel, and possibly hypernephroma. There is probably no synergistic effect betwen these therapeutic agents, but an additive effect may occur in some cases, which would give useful palliation. In a wide variety of diseases, radiotherapy and cyclophosphamide at the level of 1.4 g. weekly seems to be a safe and convenient combination. In our experience the radiation dose need not be reduced unless very large treatment fields are required.

Contraindications

1. Liver and lung metastases are rarely benefited; such patients should not be subjected to a prolonged course of therapy.

2. As the effect of this alkylating agent is unpredictable, it should not be used as the sole method of treatment in a disease where effective agents already exist.

3. Cyclophosphamide is slow in its action at the dosage levels used in our studies; it is not indicated in conditions such as superior vena caval obstruction or compression of the spinal cord due to tumour which require urgent treatment.

SUMMARY

The literature is reviewed and the reported responses of various forms of malignant disease to cyclophosphamide therapy are collected. Dosage schedules varied widely in the different series encountered in this review.

The toxic effects are depression of the bone marrow, nausea, and alopecia, although other toxic effects are occasionally described.

A personal series of 67 cases of advanced malignancy which have been treated is reported in detail, and the results are compared with those of other authors.

The probable indications for and contraindications to the use of this drug are discussed. In combination with radiotherapy it is safe and practicable, and merits wider use.

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PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

When a patient has apparently completely recovered from an acute attack of appendicitis, he may never suffer from it again, but in a certain percentage of instances the inflammation recurs. The frequency of such recurrences has been very differently gauged by different writers, and this difference of likelihood of recurrence has led to very great variation in the advice given as to the removal of the offending organ in the "quiescent period". Some authorities, such as Ochsner, believe that one decided attack is an indication for operation some three weeks after it is over, while others would wait until two or even three attacks have occurred before they would thus act. If the initial attack has been a severe one the appendix may have been destroyed by the severe inflammation, or if not, may have been so walled off by adhesions that any subsequent attack, if it should occur, would be of little danger.

Appendicectomy in the quiescent period is an operation so little attended with risk that it may be advised with little fear. No hard and fast rule can be laid down, but where an individual, who has had one well-marked attack, is apt from his occupation to be far removed from skilled surgery, it would seem wise to advise that he have his appendix removed. If, however, he lives near surgical means, then one may be justified in advising that he need not subject himself to the slight risk and several weeks of invalidism inseparable from an operation all for fear of a further attack which is as likely as not never to occur.—Robert D. Rudolf, *Can. M. A. J.*, 1: 927, 1911.

EVALUATION OF ASSESSMENT OF FOLIC-ACID DEFICIENCY BY SERUM FOLIC-ACID ACTIVITY MEASURED WITH L. CASEI*

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THE FOLIC-ACID activity of human serum may be assayed microbiologically using *L. casei*. This technique, adapted by Baker *et al.*[1] from that described by Usdin, Phillips and Toennies[2] and by Jukes,[3] has been reported to provide a reliable and convenient means of recognizing folic-acid deficiency in man.[1, 4] Because of conflicting evaluations of this technique which have been reported recently,[1, 4, 5] we have attempted to assess the reliability of this assay in detecting clinical folic-acid deficiency.

MATERIALS AND METHODS

Lactobacillus casei (A.T.C.C. No. 7469) was subcultured at weekly intervals in the maintenance medium recommended by Baker *et al.*[1]

The assay procedure was carried out exactly as described by Herbert,‡[4] with the following exceptions:

1. The assay was carried out in 20-ml. screw-capped culture tubes.
2. The serum-buffer was incubated for 90 minutes, as recommended by Baker *et al.*[1]
3. The inoculum was prepared by adding 1 ml. of a one-week culture of the organism to 10 ml. of maintenance medium, which then was incubated for six hours. (One ml. of this culture in 10 ml. of basal medium constituted the inoculum.)
4. Volatile preservative was added to the medium to a concentration of 1%. No preservative was added to the buffer. Prior to use, the medium was filtered through Whatman's No. 2 filter paper, to aid in complete removal of the preservative.
5. After incubation, the turbidity of the culture tubes was determined in a Coleman Model-14 spectrophotometer.

Crystalline pteroylglutamic acid was diluted as recommended by Baker *et al.*,[1] and kept frozen until use.

Blood was obtained in sterile syringes. After coagulation the blood was centrifuged at 1000 G., and the serum was collected and stored at –20° C. until assayed. All glassware, other than syringes, was cleaned in sulfuric acid chromate solution and then autoclaved.

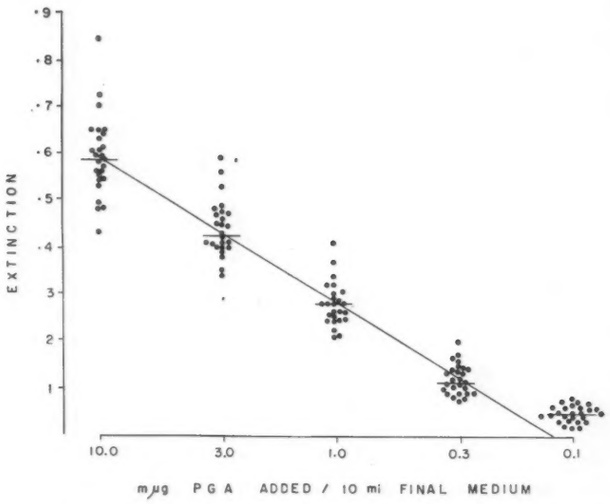

Fig. 1.—Growth response of *L. casei* to pteroyiglutamic acid in assay medium.
Growth response (optical density) of *L. casei* in the assay medium containing different quantities of added pteroylglutamic acid. These represent duplicate standard curves of alternate routine assays over five months.

Serum vitamin-B_{12} level was determined in all patients by the technique of Mollin and Ross,[6] using *Euglena gracilis* var. *bacillaris*.

The diagnosis of pernicious anemia was confirmed by the Schilling test, using 0.5 μg. of Co^{58}-B_{12}, and 48-hour urine collection with two flushing injections, of 1000 μg., 24 hours apart, as described previously.[7]

RESULTS

As shown in Fig. 1, the growth response of the *L. casei* organism in the assay medium was proportional to the concentration of folic acid added, above 250 mμg. of folic acid per 10 ml. of medium. Since, in this procedure, the test serum is diluted 1/10, this would indicate that the lowest concentration of folic-acid activity which can be determined quantitatively in serum by this technique is 2.5 mμg./ml.

In Table I, the serum folic-acid activity determined by this technique is compared to the clinical assessment of deficiency in 100 patients. Folic-acid deficiency was recognized by the presence of a megaloblastic bone marrow, with a history of deficient diet, and subsequent response of the bone marrow to hospital diet or to the intravenous injection of a small dose of folic acid. The

TABLE I.—CORRELATION OF SERUM FOLIC-ACID ACTIVITY AND CLINICAL DEFICIENCY

Serum folic-acid activity (mμg./ml.)	*Numbers of patients*		
	Normoblastic	*Megaloblastic Folic-acid deficiency*	*Megaloblastic Pernicious anemia*
≥6.0	43	—	9*
4.5 - 5.9	19†	—	6
3.0 - 3.9	6	—	—
<3.0	3	12	2

*One patient with nutritional vitamin-B_{12} deficiency included.

†One patient with rare macrogranulocyte in bone marrow (see text).

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‡The reagents used in the medium were obtained from Fisher Scientific of Canada, Limited, or from California Corporation for Biochemical Research.

single, small, therapeutic dose used was 15 μg. of folic acid per kg. of body weight, and in the six folic-acid-deficient patients so studied it induced conversion of the bone marrow from megaloblastic to normoblastic within 72 hours. In three patients with vitamin-B_{12} deficiency and normal serum folic-acid levels, this dose of folic acid did not alter the megaloblastic appearance of the bone marrow.

As shown in Table I, the serum folic-acid activity of all patients with clinically recognized folic-acid deficiency was below 3.0 mμg./ml. Three patients with normoblastic bone marrow showed apparently deficient levels. Two of these had disseminated malignant neoplasm, and their folic-acid intake had been poor. The third patient was admitted with a history of gross malnutrition but with normoblastic bone marrow.

Only one patient was found to have bone-marrow changes suggestive of megaloblastic anemia, without abnormally low serum levels of vitamin B_{12} or of folic-acid activity. This patient was admitted to hospital with marked iron deficiency (serum iron 7 μg. per 100 ml. of blood, unsaturated iron-binding capacity 412 μg. %) secondary to acute and chronic gastrointestinal hemorrhage. The hemoglobin value was 7.3 g. % and the reticulocyte count 6.4%. Serum vitamin-B_{12} level was 548 μμg./ml., and serum folic-acid activity 5.1 mμg./ml. Bone marrow showed marked erythroid hyperplasia which was normoblastic in appearance, but rare giant macrogranulocytes were found. The patient gave no history of deficient dietary intake, and made a complete recovery on iron therapy alone.

Two of the patients with pernicious anemia were found to have low serum folic-acid levels. Both were elderly women with complaints of vomiting and anorexia for one to three months, and one complained of diarrhea also. One of these patients was treated initially with vitamin B_{12}, with clinical improvement but with suboptimal reticulocytosis and a slow recovery of hemoglobin level. The other responded partially to hospital diet, but residual megaloblastic changes in the bone marrow did not disappear until she received injections of cyanocobalamin.

DISCUSSION

It would appear that the technique described for the microbiologic assessment of folic-acid deficiency, using *L. casei*, correlates well with clinical deficiency. We have found this assay to be reliable for measuring folic-acid activity above 2.5 mμg./ml. of serum. The relatively poor growth curves with added folic acid reported by Cooperman, Luhby and Avery[5] need not be interpreted as indicating that the assay is insensitive to folic-acid activity.

The clear separation between deficient and non-deficient patients by the level of 3.0 mμg./ml. would justify the use of this value to differentiate between patients with and those without clinical folic-acid deficiency.

All patients with serum values below 3.0 mμg./ml. almost certainly had folic-acid deficiency; it may be that some of those with slightly higher values but without megaloblastic marrow were similarly deficient. A number of patients in the latter group had metastatic carcinoma or gross malnutrition, but they could not be differentiated from normal subjects by single determinations of serum folic-acid activity. Serial determinations might have demonstrated a developing deficiency. Thus, with the data available, the lower limit of the normal range of serum folic-acid activity cannot be defined precisely.

Recent work from Israel[8] suggests that, using *L. casei*, the assay of folic-acid activity in whole blood may be somewhat superior to the serum assay as a measure of folic-acid deficiency. If this work is confirmed, the whole-blood method may permit a sharper distinction of the lower limit of the normal range than does the serum method.

SUMMARY

Serum folic-acid activity, determined with *L. casei*, differentiates between normal subjects and patients with clinical folic-acid deficiency. All patients with megaloblastic anemia due to folic-acid deficiency were found to have serum values below 3.0 mμg. per ml. by this technique.

We are grateful to Dr. Herman Baker for his help in setting up the assay. The technical assistance of Mrs. Violet Jew, B.Sc., is acknowledged.

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PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

Sir James Paget, in his presidential address before the Pathological Society of London in 1887, says, "Surely, it would be hard to name a discovery in biology which more deserves the name of scientific than does Jenner's discovery of vaccination; and yet it was made in the plainest, practical manner while he was a country practitioner. But, observe, Jenner was a thorough naturalist, trained by John Hunter; and I suspect that all the best advances in clinical pathology, the best not only in their utility, but in their fitness for adjustment among the largest principles of our science, have been made by practitioners who were either by nature or by cultivation men of scientific mind. And it is as sure as anything of the kind can be that similar studies by men of similar mind will still attain as good results."—A. Primrose: Address in Surgery, *Canad. M. A. J.*, 1: 610, 1911.

COMMENTS ON EMOTIONAL DISTURBANCES IN A MEDICAL UNDERGRADUATE POPULATION*

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IN THE COURSE of one calendar year, 77 out of a total of 422 medical students in the Faculty of Medicine, McGill University, are known to have sought help for emotional problems. Fifty-eight of these students were seen by the authors, 17 attended the Student Health Service because of emotionally determined somatic complaints the majority of which were hypochondriacal, and four sought treatment as private patients from psychiatrists on the teaching staff (Table I).

TABLE I.

Agencies consulted	*No. of students*	*% Total student body*
1. Medical student mental health research project	58	13.8
2. Student health service	15	3.5
3. Other psychiatrists	4	1.0
Total	77	18.3%

These figures do not represent the true incidence of psychiatric disturbance in the medical undergraduate population. For one thing, other advisory and counselling agencies exist in the University. These include both formal and informal facilities such as the University Chaplain and the Student Financial Adviser on the one hand, and the numerous medical teachers with whom the students come into contact on the other. There is no doubt that some of the students who seek help from these quarters for alleged financial, spiritual or academic problems would be recognized by the psychiatrist as having a significant degree of emotional disturbance. However, it was not possible to make a reliable estimate of how many such individuals were present in the student body. Therefore, no claim can be made that the figure 18.3% represents the upper limit of psychiatric disorder; rather, this figure is a reliable *minimal* estimate of the incidence of psychiatric disturbance in the undergraduate population. This figure is within the range of 15-20% of students who, according to Malleson,[5] consult student mental health services for psychiatric help or counselling during the course of their university career.

When the total group who received counselling were compared with their peers who did not seek this service, using 23 of the usual socio-economic variables such as religion, age, family's educational and economic status, nationality, etc., no statistically significant features emerged by which the two groups could de differentiated. This confirms the findings of Davie[1] at Yale, who showed that the student's position in either group, patient or non-patients, was not related to a similar series of socio-economic factors.

Because students seeking psychiatric help might show related academic difficulties, a control group was selected and compared with the counselled group in class rank, intelligence quotient and Medical College Admission Test (MCAT) scores. Despite significant differences in academic performance, the two groups were essentially similar in their intelligence and MCAT scores. This has been reported in detail elsewhere.[7]

Better quantitative and qualitative clinical psychiatric data are available on the 58 students who were under the care of the authors, and for this reason they will be given more detailed consideration than the remainder of the group.

Fifty-eight students came for psychiatric help after the free and confidential counselling facility was announced; 43 came of their own accord; 12 were referred by the Dean of Medicine, largely because of unsatisfactory academic performance; and three were referred by physician-teachers.

The distribution according to the year of the medical course is shown in Table II.

TABLE II.

Year of course	*No. of students*
1	21
2	14
3	18
4	5

The abrupt drop in the students from the fourth (final) year is no doubt related to the type of problem faced by the senior students. In all five, the core of their difficulties was the impending termination of their student status, and the necessity of assuming the personal and professional responsibilities of the physician (the successful attainment of which presents so many hazards to their junior colleagues).

The group who received counselling was divided into two categories: 21 students who had psychiatric problems before beginning medical school; and 32 in whom psychiatric problems developed after their entry into medical school.

Five students are not included in this classification: one had no recognizable psychiatric problem; the other four did not admit that they had any problems themselves but came with complaints about their fellow students, teachers, wives, etc. They were not sufficiently disturbed to be diagnosed as paranoid; rather they were disgruntled, and had much in common with the group of

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students that Davy[2] has described as "the Disappointed Undergraduates".

Within each of the two major categories in our classification classically recognizable clinical syndromes occur as well as situations which are not clearly defined nosologically. The divisions are somewhat arbitrary and it was uncommon when the specific problem did not have roots in the student's previous personality. However, in the cases in the first category there had been frank symptoms or evidence of personality distortion before entry; in the second category, the emotional problems reached the level of the pathological only after the student came into the medical school.

(1) *Problems Antedating Medical School*

The psychiatric disturbances recognized in this group were as follows:

Obsessive-compulsive neurosis	3
Obsessive personality	1
Neurotic depression	2
Depressive personality	4
Anxiety state	6
Sexual disability	1
Stuttering	1
Schizoid personality	1
Borderline states	2
Total	21

When a student with a pre-existing psychiatric problem enters the medical school, one of three things may happen: his symptoms may worsen; they may remain unchanged; or they may improve; and in that order of frequency. The intensification of symptoms is most often related to the student's exposure to such emotionally-laden situations as birth, death, disease and contact with the human body. Students who improve during the course do so for reasons related to their motivation for studying medicine; in medicine they find what they have been looking for. For example, a student who had hypochondriacal fears, due in part to the phantasied effects of compulsive masturbation, was led to study medicine. During his studies, he learned that masturbation does not result in bodily harm and he experienced some relief from his fears. In a few cases, pre-existing neurotic difficulties may even lead to "over-achieving"; a student with markedly perfectionistic tendencies was driven to ceaseless efforts to master his studies, with the result that he stood considerably higher in his class than his intellectual abilities would have indicated as likely. For the most part, however, as the analysis of their academic performance shows, this group is handicapped academically when compared with their peers.

None of the students in this group reported their emotional difficulties when they answered the appropriate question on the McGill Medical School application form. This question asks them to state whether they have had emotional symptoms or psychiatric treatment prior to application.

(2) *Problems Arising after Entry into Medical School*

The problems of the students in this group were further subdivided as follows:

(a) Students with problems that were related specifically to the medical school milieu or medical subjects of study, 14.

(b) Those with problems that were related to the college experience but not specifically to the medical course, 9.

(c) Those with problems that were primarily sexual and that appeared during attendance at medical school, 9.

(a) *Problems Related to the Medical Milieu*

The varieties of problems were as follows:

Acute reactive depression	1
Medical examination phobia	2
Acute dissociative reaction	1
Depersonalization episode	1
Hypochondriasis	3
Concern over role as doctor; "Should I be a doctor?"	6

The first four of these categories are reactions similar to those seen in other types of psychiatric practice and are notable only in that they occurred in response to circumstances specific to the medical milieu. One case will serve as an example.

Following a "spot" examination in which he failed, a 22-year-old student developed an acute amnesia with a memory loss covering the previous four days. This reaction was related to his ambivalence towards his medical training; the subject in which he failed was his father's specialty.

In popular thinking, hypochondriasis is the medical student's neurosis par excellence. However, this entity occurred as the major complaint in only three students, although it was a secondary symptom in several others. There are three reasons for this. First, an increased degree of concern over health is a reaction the students expect in themselves in their clinical years and it is apt to be shrugged off with a joke by the more robust. Second, students with these fears are usually quickly reassured by a negative diagnostic procedure, even if this is carried out by a classmate or themselves. Finally, those students in whom this concern is more pressing consult an internist or a surgeon rather than a psychiatrist. Most of the hypochondriacal students seek help from the Student Health Service or the clinician of their choice. Only if these measures fail do they consult the psychiatrist.

In six students, the main problem was a persistent and severe doubt about the decision to study medicine; they either doubted their capacities for the profession or doubted whether they really wanted to become doctors. In addition, this doubt was frequently mentioned as a secondary concern. With the students in whom this was the major problem, there was often a history of previ-

ous uncertainty about what they should do with their lives; some had changed faculties on one or two occasions before entering the faculty of medicine. Uncertainty about the doctor's role may be superimposed upon a more fundamental uncertainty about sexual identity. In other cases the student may have been subject to strong parental pressures to become a doctor but may himself have other interests rebelliously or covertly, or it may be part of a general negativistic pattern. As one student remarked, "If any of my friends wants to go anywhere or do anything specific, I find that I want to do just the opposite, not because I genuinely want to do the opposite, but just to be stubborn or different. Both my parents want me to be in medicine and I probably do too, basically, but I keep thinking about being something else like a taxicab driver or a teacher."

In other cases the student feels he cannot live up to the example of his teachers or their expectations of him. At other times the unpleasant aspects of medicine seem to raise doubts in the student's mind, i.e. the prospect of seeing sickness and death every day, or of handling feces and urine. This latter aspect becomes most prominent during the third year when the student embarks upon his clinical work. Generally speaking, the difficulties encountered in this group of students are very much those which Erikson[3] has characterized as the symptoms of "identity diffusion".

(b) *Problems Related to College Life*

Nine of the students had problems which were not related specifically to the study of medicine, but which were primarily reactions to college life. This group was often referred by the Dean, whom they first contacted with complaints of academic difficulties. One suffered from a language difficulty which he would not acknowledge and in several anxiety was a reaction to intelligence quotients that were barely sufficient for successful graduation. There were anxiety reactions related to financial difficulties.

(c) *Problems Not Related to the College Milieu*

Nine of the students had problems primarily related to sex that were mostly functions of their age and status. The types of problems were as follows:

Reactions to unhappy love affairs	4
Concern over possible pregnancy of a girl-friend	2
Women with concern over a masculine identification	2
Impotence	1

DISCUSSION

At McGill the Faculty of Medicine is, in effect, a postgraduate faculty and the average age of the students upon admission is 21. They are about four years older than students admitted to the larger undergraduate faculties.

Therefore, the students are young adults, as yet only partly committed to a career in medicine as, what Osler called, a "way of life". The educational efforts of a medical school should be directed to facilitating and making possible the growth and adaptation of the individual necessary to the attainment of this goal. The interaction of three groups of variables must be considered in any comprehensive attempt to observe and describe the vicissitudes of this adaptive process. These are: the student himself, including his personality, physical health, intellectual endowment and cultural background; the social and educational characteristics of the particular college setting; the study of medicine, as a process of acquiring certain skills, attitudes and knowledge.

The classification that has been employed is based on these three groups of variables. It is assumed that students who seek psychiatric help are those who are encountering some difficulty, severe or slight, transient or chronic, in the processes of a smooth adaptation. The classification permits the separation of the counselled group into three sub-groups, in each of which the action of one of the above groups of variables can be discerned as a major factor in producing the difficulties that characterize that sub-group. In effect, the classification helps one to find accurate answers to the question "What problem does this student encounter in this university pursuing this course of study?"

The faculties of medicine in different universities differ from each other in many important respects, some obvious, some subtle. This makes it a matter of some importance, as both Funkenstein[4] and Malleson[6] have pointed out, to describe, as a starting point for further investigation, what actually occurs in a given university as the student and the faculty proceed through the course together.

The present findings indicate that in 40% of the students who seek help for emotional difficulties while studying medicine at McGill, frank personality problems or symptoms, psychodynamically related to their presenting complaints, existed prior to enrolment; it is only prudent to assume that the major factor in the maladaptations of these students while in medicine was the personality they brought with them.

In the remaining 60%, the circumstances of college life or the stresses of medical training appeared to be the major factors which determined the emergence of emotional problems. In these young people their previous adjustments were efficient enough, if sometimes somewhat precarious, to avoid any real threat of disablement. This group, as it grows in numbers, should provide the investigator with an opportunity to identify and assess those aspects of the student's personality, the factors in the college environment, and the elements in the material of the medical course which interact to bring about difficulties in adaptation.

These findings are clearly reflected in the diagnostic categories which characterize the two major groups; these diagnoses were made prior to and independently of any attempt at classification. In the "befores", diagnoses suggestive of chronicity, like "personality-type," "neurosis," abound, while in the "after" group, in contrast, there occur mostly words like "acute" and "reaction".

There are further differentiating factors between the two groups. The 21 students of the "before" group, 40% of the total group, accounted for 65% of the total hours of psychotherapy given the entire counselled group, and responded in a less gratifying manner to therapeutic help. However, no statement is possible at the present time about the significance of possible differences in academic ability between the before and after groups.

CONCLUSION

Our experience with the medical students who sought psychiatric counselling indicates that 40% bring their problems with them to medical school. These problems are made worse, unaltered or made better by the medical school experience in that order of frequency. In the remaining 60%, the emotional problems encountered are in reaction to factors in the total medical school environment; of these, about half encounter difficulty with the curriculum. Further study of the latter group might lead to the formation of hypotheses concerning the complex adaptive tasks involved in medical training.

The authors wish to express their indebtedness to Dr. L. G. Stevenson, Dean, Faculty of Medicine, and Professors D. E. Cameron and R. A. Cleghorn, of the Department of Psychiatry, all of McGill University, for their kind co-operation.

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SPECIAL ARTICLE

TEN USES OF EPIDEMIOLOGY

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THE PRESENT status of epidemiology can be described as that of modern uses rather than modern concepts. Epidemiological principles were evolved at a time when infectious or infectious-like diseases were of major importance, and it is questionable whether those principles are sufficiently realistic or of general enough applicability to satisfy current needs.

It is the purpose of this presentation to examine the ways in which epidemiology can be used in order to redefine its principles. These uses are not mutually exclusive; they are not necessarily discussed in order of importance; and it is not intended to emphasize one at the expense of another. At the moment, 10 uses suggest themselves. Some already have been considered by Morris[4] and others may occur to the reader.

Because most uses of epidemiology need not be restricted to human populations, the expression "a host" is preferred to "the host" in the discussion which follows. In addition, the term "disease" includes injury and it may involve a consideration of sequelae such as disability, defect and impairment.

The ten uses of epidemiology will now be defined and discussed briefly.

1. To determine which in the three possible sets of disease factors, host, agent and environment, are important in the occurrence of a specific disease or class of diseases, the extent to which those factors are important and the manner in which they interact.

The epidemiologist obtains information about the occurrence of disease from a variety of sources, e.g., his own studies, all branches of medicine and the natural sciences including clinical medicine, demography, sociology and psychology, and any official, voluntary or private agency that collects and/or interprets pertinent data. Furthermore, he arranges the data in orderly fashion, so that whenever possible, he can analyze them by acceptable techniques. He realizes that an investigator should not employ a technique that is not designed for his type of problem or one that is not widely known without establishing a rationale for its use.

Vital statistics rates vary with age and other host characteristics. Consequently, in analyzing information on the occurrence of disease, the epidemiologist may wish to adjust for those characteristics. For example, by applying the age specific rates

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of groups being compared to a standard age distribution, he can eliminate age as a source of variation in overall rates and thereby study the effects of other factors. However, such adjustments are not entirely foolproof and should be interpreted with caution.[7]

It should be apparent from the foregoing discussion that the epidemiologist and clinician do not function independently. The epidemiologist cannot study the occurrence of certain diseases unless the clinician supplies him or the health department with case records; the clinician may find it difficult to make an adequate diagnosis unless he is provided with information regarding the occurrence of disease by age, by sex and by any other factors that may help to characterize a disease.

2. To study the occurrence of disease in a population for purposes of community diagnosis and prognosis.

A clinician sees a disease as it occurs in an individual; he obtains a history, examines his patient for signs, symptoms, laboratory and radiological findings and then makes a diagnosis. The physician is concerned not only with the diagnosis but the prognosis as well. As a clinician, he does not deal exclusively with the sick, but must study normal subjects in order to recognize the sick. In addition, some of his patients are well persons.

The epidemiologist is interested in the individual, too, but his attention is primarily directed toward the group, in this instance, the community at large. Through morbidity, mortality and population data, contained in existing records or collected in his own surveys, he determines which diseases are prevalent in a community and whether as single entities or in association with each other they are severe enough to endanger the health of the community. Of course, his diagnosis also depends on a knowledge of the reaction of a society to certain diseases and on information regarding the unafflicted, for they are part of the community as well. The prognosis in a community illness is based on similar experience elsewhere or in the same community at an earlier date and on the availability of means to cope with the problem.

The severity of disease in a community can be gauged by several indices: whether it is a leading cause of death; whether its prevalence attains highly endemic or epidemic proportions; whether it has a high case fatality or other measure of complications; whether it is a source of mass hysteria and panic; whether it involves a large proportion of the young; whether it leaves permanent disability, defect or impairment; whether it adversely affects the economic status of a community; whether it contributes to excessive absenteeism in essential industry; or whether it requires extensive mobilization of resources.

For reasons cited above, the role of the epidemiologist can be described as that of a *community diagnostician.*

3. To describe the epidemiology of a disease or class of diseases.

Facts or events relating to the occurrence of a disease (or class of diseases) constitute its *epidemiology.* The occurrence of a disease and its severity and outcome are resultants of a complex of interacting factors, some of which are host factors and others, agent and/or environmental. A description of the epidemiology of a disease involves a thorough study of that disease in all its aspects including its frequency in various populations and subpopulations, and known and suggested factors in the *premorbid, morbid* and *postmorbid* periods. Furthermore, gaps in knowledge are bridged by reference to animal studies, postmortem examinations and observations on healthy carriers and medically and surgically treated patients. The description may contain information on age, sex, race, social class, occupation and agent and environmental characteristics. Information can be expressed in *qualitative* terms, presented *graphically,* arranged in *tables* or summarized in *averages, proportions* and *measures of variation.*

The *premorbid period* is the period preceding the inception of a disorder, the *morbid period,* the pathological and clinical course and the *postmorbid period,* the aftermath. *Pathogenesis* is a term usually restricted to the early stages of the morbid period, although it can be applied to the premorbid period, inasmuch as disease does have its origin in events that antedate pathological changes in a host.

A disease is initiated at the cellular or functional level. The point at which it becomes manifest or detectable will depend on the disease and the sensitivity of its indicators, this can be labelled the *clinical horizon.* A disease may be aggravated or relieved and at times stationary or arrested.

"Natural history" is an expression inherited from the past. It imparts a mystical quality to disease which may suggest something more than a study of occurrence.

4. To measure risk.

When the denominators are appropriate, the epidemiologist may use rates of the type listed in parentheses. These rates approximate the separate probabilities that, under conditions similar to those in which the rates were derived, a person will acquire a particular disease during a given period of time (*attack rate,* morbidity rate, case incidence rate); have a particular disease at a given point in time (*prevalence rate*); die of a particular disease during a given period of time (*mortality rate,* death rate); or if he has a particular disease, that he will die of it during a given period of time (*case fatality rate*). Such probabilities are measures of risk and they are useful in prognosis and for actuarial purposes.

5. To study the occurrence of disease or death with time as a variable. Such a study is referred to as a *historical* study.

In historical studies, it often is convenient to speak of trends, namely, *secular* trends and *cyclic* trends. A secular trend ranges over a long period such as a century, and portions of it may increase, decrease or remain stationary. A cyclic trend must exhibit periodic fluctuations regardless of its duration; consequently, it is a trend within a trend. For example, in the United States at least, the monthly death rate for all forms of tuberculosis usually reaches a peak in late winter or early spring and falls to a low point in late summer or early fall. A plot of monthly rates computed on an annual basis[3] shows a series of alternating waves or spikes. However, the annual rate has declined almost continuously since 1900.

Certain distributions of the population change over time; it may be necessary to allow for those changes in order to make meaningful comparisons. For example, the age distribution of the population changes over time but the sex distribution, on the other hand, remains fairly constant.

Epidemics may recur in cycles[6] with the amplitude of a spike representing the height of an epidemic and the period intervening between spikes, the period of endemicity.

6. To aid in the search for causes of disease.

The mechanism of disease production is so intricate that causes are not easily isolated, and it may be advisable from a public health point of view to work with assumed causes. An assumed cause may be nothing more than a correlate of a cause.

In general, a *cause* can be defined as an agent or any host or environmental factor that is influential in producing disease or accelerating its appearance. It is beyond the scope of this presentation to indicate what type of evidence is necessary to establish a cause. In cancer and arteriosclerosis, the evidence is chiefly circumstantial.

Although all agents and certain host and environmental factors can be described as causes of disease, it is their interactions that produce the effect. The consensus today is that all diseases have more than a single cause. This is the concept of *multiple causation*. Host susceptibility varies from one individual to another and in the same individual. As far as can be determined, one or more agents and/or the environment must also play a part. Therefore, it would be improper to speak of "the" cause of a disease. "A" cause is preferred, and each cause is a *contributory* cause regardless of its relative importance.

Studies on causes of disease are often futile attempts to discover agents. Not only must an agent be influential in producing disease or accelerating its appearance, but it must exist as an entity and not to be confused with a host or any of his characteristics. Conceivably, there are diseases in which none of the causes conform to this description and others in which conventional agents are elusive.

Multiple causes need not imply multiple agents, though some diseases have multiple agents as well. (Multiple agents act together or alone.) For example, primary cancer of the lung may have a rather diverse etiology. Several host and environmental factors have been implicated, and many substances are suspected of being agents. These include age, sex, heredity, nutrition, chronic infections resulting in metaplasia and scarring, viruses, hormones, tobacco smoke, occupational exposure to nickel, chromates, asbestos, inorganic arsenic and radiation, and air pollution produced by fumes from motor fuels and the incomplete combustion of coal.

In spite of this, some people still believe that tobacco smoke is the only cause of lung cancer. These facts cannot be disputed: tobacco smoke is not a proven cause; and persons who never smoke also develop this disease. For reasons such as these, it must follow that the probability that an individual with a certain characteristic will develop a disease is not necessarily the probability that he will develop the disease as a result of being exposed to a substance identified with that characteristic unless it is known unequivocally that no other substance or environmental factor is a cause of the disease in the same species.[5] The above wording has been carefully chosen to preserve the notion of *competing risks* in disease etiology.[1, 2]

Another matter of practical importance is ascertaining whether an agent is a cause of a disease in a given individual. A suggested criterion is this: An agent cannot be said to be a cause of a disease in a given individual unless it is known with a reasonable degree of certainty that the disease would not have occurred when it did without the agent. Therefore, it would be virtually impossible at the present moment to state, for example, that radiation definitely was a cause of leukemia in a given individual.

When a substance is not a proven cause, the terms "possible" and "probable" seem in order when the evidence is suggestive. The choice of the proper term would depend on the strength of the evidence. However, when a substance is not a proven cause, it would be of little or no consequence to argue further that it is a possible possible cause or even a probable probable cause in a given individual.

7. In disease prevention and control.

The epidemiologist helps to control a disease when he identifies it, describes its epidemiology, demonstrates its existence in a community and investigates its source.

Primary control or disease prevention is the ideal control measure. *Secondary control* consists of diagnosis and treatment, and *tertiary control* involves rehabilitation of the disabled and correction of defect or impairment. It is interesting to note that primary control is peculiar to the premorbid period, secondary control, the morbid period and tertiary control, the postmorbid period.

The objectives of primary control might be summarized as follows: (1) to modify or remove the

causes of disease, (2) to keep the causes from interacting, and (3) to diminish the intensity of the interactions.

8. To aid in the identification of clinical syndromes.

A syndrome is a group of signs and symptoms that occur together and characterize a disease. Some diseases closely resemble each other in signs and symptoms. The object is to distinguish among these diseases on the basis of their subtle peculiarities. This falls within the domain of *differential diagnosis*. Problems of this nature are of frequent concern to the epidemiologist, especially since they are important in case finding.

9. To aid in the detection of presymptomatic and latent disease.

Many diseases such as tuberculosis, diabetes, hypertension, glaucoma, cancer of the cervix, neoplasms of the lung and syphilis can be detected before the onset of symptoms or the development of serious changes. The way to accomplish this is through mass screening techniques (both mono- and multiphasic), pre-employment physical examinations, periodic health examinations, special surveys and routine examinations in hospitals and clinics.

10. In administrative medicine and operations research.

One might evaluate the success of a disease control program; the needs of a hospital in terms of equipment, personnel and space; the quality of medical care in a community; and the efficiency of hospital administration as compared with private industry. These are areas in which the investigative experience of an epidemiologist may prove rewarding.

DISCUSSION

Directly or indirectly, the control of disease is a universal effort involving nearly every science and vocation. The science of epidemiology is an integral part of that effort, for its interests are diversified and far-reaching. Nevertheless, there are certain similarities between clinical medicine and epidemiology that need be emphasized in conclusion.

Although the clinician and epidemiologist have a different approach to the disease problem, their objectives are essentially the same. The purpose of the clinician is to understand the nature of disease, so that he can prevent it, recognize it, predict its behaviour and treat it on an individual basis. When a cure is not possible, he attempts to limit the extent of disability, defect or impairment and forestall death. The purpose of the epidemiologist is to understand the nature of disease, so that on a community-wide basis, it can be prevented, its severity and prognosis assessed and further control measures instituted. When control measures are taken, the spread of a communicable disease may be checked, or if a disease is not communicable, its onset in susceptible individuals may be delayed or indeed prevented. Thus, the epidemiologist has a responsibility for the control of coronary artery disease and lung cancer as well as typhoid fever, diphtheria, yaws and schistosomiasis.

In essence, then, the clinician and epidemiologist diagnose, prognosticate and control. The clinician also treats, but treatment is a means of control. Both describe and engage in research. Diagnosis, prognosis, control, description and research are areas in which mathematics and statistics play an important if not a necessary role.

COMMENT

The following definition of epidemiology is suggested in its uses: Epidemiology is the science that is concerned with all factors relating to the occurrence of disease, and incidentally death, where the term "disease" includes injury and it may involve a consideration of sequelae such as disability, defect and impairment.

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PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

Dr. T. H. Whitelaw, Edmonton, said that in Edmonton much has been accomplished towards obtaining a supply of fairly pure milk. If the dairy by-law at present in force could at once be strictly enforced, the public would be assured of a supply as nearly equal to certified milk as it is possible to obtain. He said that much difficulty had been found in persuading the average milk-man that it is his duty to co-operate with the health department in obtaining the best results, and that this co-operation would eventually result in direct benefit to the milk producer, as well as to the consumer. In Winnipeg, a trained dairy inspector is employed at a salary of fifteen hundred dollars per year, who inspects all dairies and dairy farms at least once a month. The standard for butter is fixed at thirty-five per cent., and a comparative test is made by straining a given quantity of each sample through an absorbent cotton disc, which clearly indicates which dairyman is carrying out the by-law in its minor details, to prevent gross dirt from gaining access to the milk pail. These discs are kept on exhibit, and the dairymen are invited to inspect them from time to time, and to take an intelligent interest in improving their methods, so as to obtain a disc freer from visible dirt from month to month.—*Canad. M. A. J.*, 1: 654, 1911.

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MEN AND BOOKS

SHERLOCK HOLMES AND MEDICINE*

DOUGLAS GUTHRIE, *Edinburgh, Scotland*

EVERYONE knows, or at least has heard of, Sherlock Holmes, the most real character in fiction. So real has he become that many people believe that he actually existed, and was not merely fictitious.

Societies have been founded in many countries to pay tribute to his memory. His sayings and doings have been studied from every angle, and the original stories regarding his life and work have formed a pattern for subsequent "thrillers". Every visitor to London who has read the tales is eager to see Baker Street, and letters addressed to "Mr. Sherlock Holmes, Baker Street, London" still baffle the authorities at the General Post Office.

Sherlock Holmes has a special appeal to members of the medical profession. The doctor, reviewing the signs and symptoms which guide him to a diagnosis of his patient's malady, has much in common with the detective who studies the clues which guide him to a solution of the crime he investigates. Besides this, the author, Conan Doyle, was a medical man, as also was Joseph Bell, the model from which Doyle drew the character of Sherlock Holmes, and more than twenty medical men make their appearance in the pages of the famous stories, though most of them allow us only a brief acquaintance with their doings.

The Author and his Models

Dr. (later Sir) Arthur Conan Doyle was born at Edinburgh in 1859 and graduated in medicine at that University in 1881.

He was conducting a small general practice at Southsea when he wrote his first book "A Study in Scarlet", in which he introduced Dr. John H. Watson to Sherlock Holmes, and those two famous characters to the reading public. The idea of making a detective the hero of a tale had already been exploited by Edgar Allan Poe ("The Murders in the Rue Morgue", 1841), and by Wilkie Collins ("The Moonstone", 1868), but Conan Doyle went a step further by developing the new technique of portraying, in each of a long series of stories, the same two characters; one, Mr. Sherlock Holmes, the Prince of Detectives, the other Dr. Watson, who acts as the Boswell and records the various adventures.

This famous partnership was continued throughout the sixty stories, four of them long, and fifty-six short, which appeared as books, or as items in the *Strand Magazine*, during a period of forty years.

The demand for the first of the "Adventures", in the Strand Magazine of May 1891, was enormous and widespread. Holmes and Watson were already popular figures, having made their reputation in "A Study in Scarlet" (1887) and "The Sign of Four" (1890).

"The Adventures of Sherlock Holmes" consisted of 12 episodes, and was reprinted in book form in 1892; The Memoirs, with 11 episodes, in 1894. Each episode or tale was complete in itself.

The last Memoir was the tragic story of how Holmes met his death as he grappled with the criminal Professor Moriarty, and both were precipitated over the cliff at the Reichenbach Falls in Switzerland. The author, Conan Doyle, had killed his hero, and great was the consternation, and even anger, on the part of many readers. "You brute, how could you?" wrote a lady enthusiast.

Perhaps the reason was that Doyle was becoming a little tired of being regarded as only a writer of detective stories. He wished to become acclaimed because of his historical novels. He had written several, and was eager to continue. But the public insisted that he should remain a writer of detective fiction.

It has ever been so. Dr. Doyle gave up practice when he turned his attention to literature, and many another medical man has had this experience. If a doctor wishes to write some work not exclusively medical, he had best do it under an assumed name. Thus Doyle found it worth while to change his profession, but even then, the public would not admit that he could shine in two different fields, in historical novels as well as detective tales.

Accordingly he was obliged to restore Holmes to life, or rather, to explain how he had had a miraculous escape from death, in order to satisfy the insistent demand of his readers for further exploits. So "The Hound of the Baskervilles" was published in 1902, and the series of shorter tales was resumed in the *Strand Magazine*, and eventually reprinted in three more books entitled "The Return of Sherlock Holmes" (1905), "His Last Bow" (1917), and "The Case-Book of Sherlock Holmes" (1927)—in all, 33 further tales.

It is generally acknowledged that the later tales are not as good as the earlier series. Holmes had recovered after his disastrous encounter with Moriarty, but he was never quite the same man.

In the meantime, Conan Doyle had continued his other literary work, had contested a seat in Parliament, and had espoused the cause of spiritualism and lectured extensively in its defence. His knighthood had been awarded in 1902 for his services in the South African War. He died in 1930 at the age of 71. Such, in brief, is the story of the author and his work.

*Address to the Vancouver Medical Association, sponsored jointly with the Department of the History of Medicine and Science, The University of British Columbia, June 17, 1961.

It is necessary to add a few words regarding the models or originals of Holmes and Watson. Watson is supposed to be the recorder, and some have concluded that Doyle based this character upon himself.

He acknowledged, however, that his description of Sherlock Holmes and his work was inspired by one of his teachers when he was a medical student at Edinburgh.

The Influence of Joseph Bell

Dr. Joseph Bell was the teacher who inspired in the mind of his pupil the idea of the greatest detective in fiction. In May 1892, when the enthusiasm for Sherlock Holmes was at its height, Conan Doyle wrote to his old teacher, "It is most certainly to you that I owe Sherlock Holmes, although, in the stories, I have the advantage of being able to place him in all sorts of dramatic situations."

Then followed a correspondence in which Dr. Bell suggested that a "bacteriological criminal" might be a good idea, but Conan Doyle replied that "the only fear is lest you get beyond the average man, who won't be interested unless he thoroughly understands".

Nevertheless Doyle continues, "I should be very grateful for any 'spotting of trade' tips, or anything else of a 'Sherlock Holmesian' nature."

Dr. Joseph Bell came of a long dynasty of surgeons. His great-grandfather, Benjamin Bell (1749-1806), was the first in Edinburgh to restrict his practice to surgery. Benjamin Bell became surgeon to the Royal Infirmary at the age of 24, and wrote "A System of Surgery", in six volumes, which had a wide circulation and was translated into French and German.

Joseph Bell, "Joe Bell" to his students, was born in 1837, and became assistant to Professor James Syme, Lister's teacher and father-in-law. Joseph Bell, like his great ancestor, became surgeon to the Royal Infirmary, and later, he was the first surgeon to the Royal Hospital for Sick Children, 1887-97, and President of the Royal College of Surgeons of Edinburgh.

He excelled as a teacher, and taught the students much else besides surgery, as he was wont to diagnose not only the disease or injury, but also the occupation and personal characteristics of each patient. Seated in his chair, his finger-tips pressed together, he would study closely the gait, expression and mentality of each patient, and would surprise both patients and students by the accuracy of his deductions. It might have been Holmes addressing Watson, when Bell taught his students the importance of the observation of trifles.

The comparison, however, ends there. Holmes had some habits which were quite foreign to Joe Bell—his incredible untidiness, addiction to tobacco and even cocaine, music at strange hours and indoor revolver practice, all belonged to Baker Street and were unknown at Melville Crescent, Edinburgh. The writer, as a junior medical student about 1905, remembers seeing Bell driving in his carriage and pair, a tall, stately man with aquiline features and alert expression: much beloved by colleagues and patients, and revered by students.

A study of hands and finger nails revealed to him the nature of a man's craft, the colour of the mud on his boots indicated a certain district of the city, wood shavings or metal filings in folds of clothing, dialect or manner of speech; each had its tale to tell.

So much for the real live author, and the real persons who may have been his original models. Before discussing some other relationships between detectives and doctors, let us glance at the background against which the dramatic tales are portrayed.

The Victorian Scene

One of the attractions of the Sherlock Holmes stories is the author's vivid description of the London of Queen Victoria. In the centre of the stage are the rooms tenanted by Holmes and Watson at Number 221B Baker Street, an address which has hitherto defied all efforts to identify the house.

I have explored the district like many another admirer of Sherlock Holmes. Much of the street was destroyed by enemy action in 1941, and has been rebuilt, but I agree with those who allege that the number was really No. 111, about the centre of Baker Street. This house is directly opposite No. 118, from which Holmes' enemy fired with a rifle at his shadow when visible on the window blind, though it actually was a wax model of his head, as those who have read the story will remember.

Be that as it may, the opening scene of each tale grips the reader's attention. One can almost see V.R. picked out on the mantelpiece by revolver shots, the unanswered letters transfixed by a jack-knife, the tobacco in a Persian slipper. Outside (let Watson now continue) "the wind howled down Baker Street, and the rain beat fiercely against the windows. It was strange here in the very depth of the town, to feel the iron grip of Nature. To the elemental forces, London was no more than the molehills that dot the fields." On another day, "A thick fog rolled down between the lines of dun-coloured houses, and the opposing windows loomed like shapeless blurs through the heavy yellow wreaths. Our gas was lit, and shone on the white cloth, and on the glimmer of china and metal, for our table had not yet been cleared."

Again, this time in summer, "It was a blazing hot day in August. Baker Street was like an oven, and the glare of the sunlight on the yellow brick-work was painful to the eye."

In some of the opening scenes there is a casual allusion to an unrecorded case. But soon the problem appears on the scene, as a letter or a telegram (there were no telephones then), or the arrival of a distracted client, or, it might be, a clue such as

the hat in "The Blue Carbuncle," or Dr. Mortimer's cane in "The Hound of the Baskervilles".

Then the two friends set forth in a cab or a hansom, or travel by rail to the seat of the trouble, which was seldom a murder, and not always even a crime, but just a problem.

In the first 12 adventures, there are only three murders.

The scene of the exploits is not always London; indeed the action is confined to London in only 19 of the 60 stories. Often, the reader is taken to the Home Counties; Surrey is the favourite ground. On two occasions the scene is laid in Norfolk; on two others, in Dartmoor. We may even find ourselves in Aldershot or Birmingham, or may discover Holmes and Watson on holiday in distant Cornwall when confronted by a problem. Yorkshire was the most northerly of Holmes' journeyings. Twice he was called to the Continent, but we are sorry that he never visited Scotland, where Dorothy Sayers found such a good background for adventure, as also did John Buchan.

Holmes did not visit Edinburgh, the early home of Conan Doyle, as well as that of Dr. Joseph Bell, the Holmes original.

In 10 of the 23 tales in the Adventures and Memoirs, the action begins in the rooms occupied by Holmes and Watson in Baker Street, but after Dr. Watson settles in practice in the Paddington district, and marries, five of the tales open with Watson calling on his friend Holmes, while in two of them, "The Blue Carbuncle" and "The Red-headed League", the story begins with the words "I had called . . . ."

A more dramatic beginning was the occasion when Watson, in visiting an opium den in London to rescue one of his patients who was an addict, finds Holmes there, disguised as an opium smoker, and in search of a missing man, the "Man with the Twisted Lip", as the tale is entitled.

"The Adventure of the Reigate Squares" commences when Watson is summoned to find Holmes lying ill at Lyons, and brings him home to recuperate in the house of Colonel Hayter at Reigate.

On three occasions, it is Holmes who calls on Watson to invite his co-operation. There are also two tales regarding earlier cases, related to Watson by Holmes as they sat together by the fire one winter's night. Although Watson is the narrator of all the early stories, two of the later ones, "The Blanched Soldier" and "The Lion's Mane", appear as though written by Holmes himself.

Of course Holmes was well qualified to write. He had already published a treatise on The Ashes of Various Tobaccos, enumerating no less than 140 varieties of cigar, cigarette and pipe tobacco, with coloured plates to illustrate the different appearances of the ashes. We also know that after his retirement to Sussex, he wrote a book entitled "A Practical Handbook of Bee Culture", which he called "the fruit of my leisured ease" ("His Last Bow").

Throughout the entire series of tales, the atmosphere of Victorian times is well preserved, and this seems to add to the interest. In every tale, we are conscious of the trappings of the time—the gas lamps, the clanging door-bells, the sound of horses' hooves, and four-wheeler cabs, the dark lanterns and the golden sovereigns. Holmes knew nothing of microscopy or of modern psychiatry, or even of finger-prints. X-rays were not discovered until 1896. His outfit was simple, a magnifying glass and tape-measure, a hunting crop and a revolver.

Among his addictions was tobacco. He was an inveterate pipe smoker, and he alleged that a concentrated atmosphere aided a concentration of thought—a statement with which few would agree today. We may let that pass, and leave him to his "three-pipe problem", but we really must protest when the author tells us that Holmes was addicted both to morphia and cocaine.

"What is it today?" asks Watson in "The Sign of Four"—"cocaine or morphine?" (Three times a day for many months he had witnessed the performance.) "It is cocaine," he replies; "would you care to try it?"

We might allow him the morphine, remembering that De Quincey, Coleridge, and others, were opium addicts.

At cocaine, however, we draw the line. We have the authority of A. R. Cushny for the statement that "The cocaine habit leads more rapidly to mental and physical deterioration than the morphine habit." Conan Doyle once said that "You must not make your detective too human," so perhaps we should not grudge Holmes his cocaine.

It is a relief to find Watson writing in the tale of "The Missing Three-Quarter"—"For years I had gradually weaned him from that drug mania which threatened once to wreck his remarkable career."

Detection and Diagnosis

There is a close kinship between the work of the detective and that of the medical practitioner. The former looks for clues which will point the way to the criminal; the latter, for signs and symptoms which enable him to make a diagnosis, or, more important still, to give a prognosis, or forecast of future events.

The importance of clear logical reasoning in medical work is not always fully recognized. Another Holmes, one of real life, Oliver Wendell Holmes, observed that "medical logic does not appear to be taught in our schools". The great physician of the 18th century, Thomas Sydenham, replied to Sir Richard Blackmore, who asked him to name a good text-book of medicine: "Read 'Don Quixote', a very good book." I can remember our Edinburgh Professor of Surgery, Professor Chiene, saying, when a student put to him a similar question—"Try the Sermon on the Mount; there is nothing better."

For my own part, I would counsel students to study Sherlock Holmes and his methods. Good

detective tales supply a lesson in logic. The doctor is a kind of detective, and he does well to follow the principles laid down by Sherlock Holmes. Even from the simple-minded Watson he may learn; Watson the humble narrator who must remain in the background in order to emphasize the more erudite Sherlock Holmes.

Watson was often surprised by Holmes, and often deceived. When in "The Dying Detective", Holmes pretends to suffer from a rare tropical disease, disguising himself with bee's wax and vaseline, Watson is completely baffled, and Holmes remarks to him, "You are a practitioner of limited experience. What do you know of Trapanuli Fever, or of the Black Formosa Corruption?" The real fact was, of course, that neither ever existed.

Holmes was a master of disguise. Three years after his presumably fatal encounter with Moriarty, when he appeared before Watson as an old bookseller in a London street, and made himself known, Watson "fainted for the first and only time in his life".

You may remember other disguises used by Sherlock Holmes: a venerable Italian priest, an unshaven French ouvrier, a drunken groom, a non-conformist clergyman.

Clever as were his physical changes of person, his alert brain and his simple logical reasoning are even more admirable.

His scathing indictments of poor Watson were many. "Elementary, my dear Watson" has now passed into common use. "I can see nothing," said Watson on one occasion. "On the contrary, Watson," retorted Holmes, "you see everything. You fail, however, to reason from what you see."

The subtle difference between seeing and observing was a favourite theme of Sherlock Holmes.

"However did you see that?" said the Police Inspector, as Holmes pointed to a hole in the window sash. "Because I looked for it," was the reply. This leads us to mention the importance of little things, upon which Sherlock Holmes repeatedly insisted: "You know my method; it is founded upon the observance of trifles" ("The Boscombe Valley Mystery"). "The little things are infinitely the most important," Holmes remarked in "A Case of Identity", and in the same tale, he advised Watson to "Never trust to general impressions, but concentrate upon details." Another of his maxims, revealed in "The Reigate Squares", was that he made a point of "never having any prejudices, and of following docilely wherever fact may lead me".

All these counsels and pithy sayings may be applied with equal significance in the practice of medicine, although spoken by the greatest detective of fiction.

Of course they are not all original. Lister was fond of telling his students that "success depends upon attention to detail", and Sir William Gull, a leading London physician a little more than 100 years ago, insisted that nothing which concerned the well-being of the patient was too minute for the doctor's attention.

Sherlock Holmes and the Doctors

It is perhaps unfortunate that the twenty or more medical men associated in some way with Sherlock Holmes flit so rapidly across the stage and are lost to view.

There was old Dr. Farquhar, from whom Watson bought a practice, Dr. Verner, to whom he sold it, and Jackson and Anstruther, who acted for Watson when Holmes called him away from his medical work.

We have been given only brief glimpses of Sir Leslie Oakshott, the surgeon who attended Holmes when he was assaulted and nearly killed, and Dr. Moore Agar, who advised him to take the complete rest he so much needed.

Two fleeting figures are Dr. Barnicott, collector of Napoleonic relics, and another collector, Dr. Hill Barton, who appears as a complete fiction on a visiting card handed to Watson by Holmes, so as to give him an "alias".

Other medical men in the Adventures and Memoirs are Dr. Percy Trevelyan and Dr. James Mortimer who came to Holmes as clients.

On one occasion the murdered man was a doctor, Dr. Ray Ernest, and in two of the stories the criminals were doctors, Dr. Grimesby Roylott, in "The Speckled Band", one of the best of the short tales, and Dr. Leon Sterndale, who in "The Devil's Foot" used a West African root to get rid of his victim.

Two other doctors appear, but not doctors of medicine, Dr. Huxtable of "The Priory School", who was a Ph.D., and Rev. Dr. Shlessinger, a D.D. who, but for Holmes and Watson, would have poisoned Lady Frances Carfax. Sir James Saunders, "the austere figure of a great dermatologist", Dr. Ainstree, "a world authority on tropical disease", Dr. Wood, the village practitioner at Birlstone, Dr. Ferrier of Woking, Dr. Richards and Dr. Horsom, are other fleeting figures in the stories.

Holmes is always in the centre of the picture, and perhaps that is why Watson did not appear to advantage, and the other doctors made such temporary appearances.

Reconstructions and Researches

Seldom in the history of literature has so much liberty been taken with the original text as with the Sherlock Holmes tales. Time and again, the chronology has been investigated, so that each story has been dated and re-dated. It is a fascinating game, or cult. From the facts as stated, the lives of Dr. Watson and of Mr. Sherlock Holmes, and even those of Mycroft Holmes his brother and of Mrs. Hudson his landlady, have been reconstructed and written.

As for Holmes, where did he go during the years of disappearance, from 1891 until 1894?

What was his relation to Mrs. Hudson, if any?

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Or to one of the few women he admired, Irene Adler? Irene Adler, then aged 101, wrote to the "Scotsman" at the time of the Conan Doyle Centenary in 1959, telling us that "dear Sherlock" died in her arms at the age of 100, after his long years of retirement, and pre-occupation with bee-keeping on the Sussex Downs.

It has been alleged that Holmes and Moriarty were the same person. As for the number of unpublished stories which have come to the light of print in recent years, they are legion.

Numerous editions of the stories have been printed, and remain in steady demand. Naturally, they are now obviously "dated". But few of the imitators have ever produced any detective stories quite so good. "Sherlock Holmes" may still be confidently recommended to all readers, and especially to medical readers. There is as yet no sign of any lessening of his popularity.

21 Clarendon Crescent,
Edinburgh 4, Scotland.

CASE REPORTS

PORTAL VEIN THROMBOSIS ASSOCIATED WITH MYELOPROLIFERATIVE ANEMIA*

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AMONG the myeloproliferative disorders polycythemia vera is known to be associated frequently with the complication, spontaneous venous thrombosis. In this disease the greatly increased red cell mass and the increased viscosity of the blood is usually accepted as the principal cause of the thrombotic tendency. A similar predisposition is less often noted in patients suffering from other myeloproliferative disorders in which increased blood viscosity does not exist.

The present report deals with the association of portal vein thrombosis, evidence of a more generalized tendency to intravascular thrombosis and a myeloproliferative disorder characterized by hyperplasia of the bone marrow, myeloid metaplasia of the liver, spleen and lymph nodes, and a peripheral blood picture showing anemia, a leukemoid reaction and, at least, a qualitative morphologic disturbance of platelets.

The patient was a 58-year-old white woman who was admitted to hospital on February 25, 1961, 14 hours after the onset of severe abdominal pain and hematemesis. She was in a state of profound shock.

Her previous history was as follows: She had experienced indefinite epigastric pain for one month in 1958. At that time, radiological examination of the upper gastrointestinal tract and of the gallbladder was negative. Later, in 1960, she complained of abdominal distension and rumbling. She lacked energy and had lost approximately 25 lb. in weight over an 18-month period. In 1960, her spleen was palpable and liver function tests were abnormal, including a three-plus cephalin cholesterol flocculation value, and bromsulphalein test showed 15% retention after 45 minutes. At that time the hemoglobin was 74.3%; the erythrocyte count was 3,200,000 and the leukocyte count was 12,000 per c.mm. The platelet count was 221,000 per c.mm., and a repeated direct count showed 332,000 per c.mm.

An episode of epigastric pain of sudden onset developed on February 24, 1961, and the patient began to vomit considerable quantities of blood. When she was admitted to hospital she was very pale, and there was clotted blood around the mouth and nose. The blood pressure and pulse were unobtainable, but when a drip of metaraminal bitartrate (Aramine) was set up the systolic pressure rose to 70 mm. Hg. The abdomen was distended, but the liver edge was palpable, in the opinion of one observer, and the spleen descended two fingerbreadths below the costal margin.

Now, the hemoglobin was 6.6 g. % with a leukocyte count of 37,925 per c.mm.; the differential count was 48% neutrophils, 35% stabs, 1% metamyelocytes, 1% myelocytes, 11% lymphocytes and 4% monocytes. A peripheral blood smear showed that the red cells were fairly well filled with hemoglobin; there were only a few microcytes, occasional poikilocytes and occasional nucleated erythrocytes. A few large platelet forms were reported, but nuclei of megakaryocytes were not seen.

Intravenous therapy, including blood transfusions, was instituted; the hemoglobin rose to 9.2 g. %, but a second leukocyte count was still 54,300 cells per c.mm. When the patient's condition had improved slightly, she began to complain of severe abdominal pain and she required sedation. For some hours her condition remained unchanged, but then her breathing became more laboured and fresh blood was present in the material being suctioned from the stomach. Gradual deterioration followed, and she died 28 hours after admission.

At autopsy, blood was found in the esophagus and in the mouth, and aspirated blood was present in the trachea and major bronchi. In the esophagus there

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were numerous tortuous, congested venous channels coursing beneath the epithelium, and in the lower third there were areas of ulceration. Fresh, clotted blood was loosely adherent to some of these areas. Blood was present in large quantities in the gastrointestinal tract as far distal as the descending colon.

The portal vein was completely occluded by a firm, well-organized thrombus which extended back up the full length of the splenic vein and into the superior mesenteric vein. Collateral venous drainage was provided by a number of dilated and plexiform veins.

The liver weighed 1250 g. and although small, was normal in consistency. On the other hand, the spleen was grossly enlarged, weighing 1150 g. On section, it was dark and congested, with no localized features visible on the cut surface, and around the periphery there were a number of freshly infarcted areas.

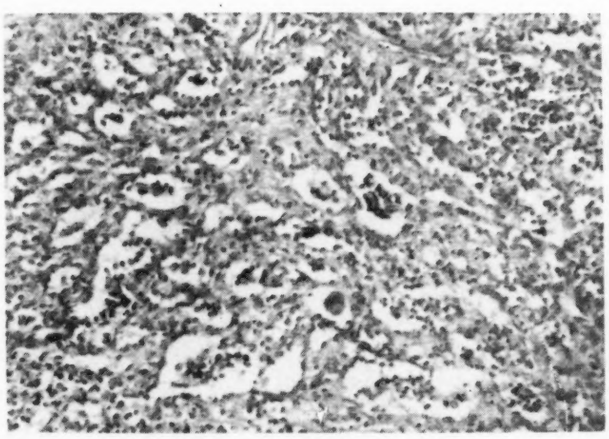

Fig. 1.—Section of spleen showing widely dilated sinuses with numerous foci of hemopoiesis.

During the examination, left ventricular hypertrophy and several uterine fibroids were noted, but there was no evidence of tuberculosis or carcinomatosis.

On microscopic examination, many of the small tributaries of the splenic vein within the organ itself contained extensions of thrombus. There was diffuse fibrosis of the spleen, and the sinuses of the red pulp were dilated and prominent. The endothelial cells lining these sinuses were enlarged and hyperplastic, and throughout the spleen there were small, diffuse and frequent foci of hematopoiesis (Fig. 1). In these foci, megakaryocytes in varying stages of differentiation were always prominent. Granulocytes and their precursors were numerous, and there were scattered groups of normoblasts.

In the liver there were similar though less frequent foci of myeloid tissue. There was a minimal increase of periportal fibrous tissue, but the hepatic architecture was well preserved and there was no destruction of hepatic parenchymal cells. A similar preservation of architecture was seen in the lymph nodes, but here too there were discrete foci of hematopoiesis. In all of the extramedullary sites, the myeloid tissue was within the sinusoids predominantly (Fig. 2).

Numerous megakaryocytes, presumably trapped by the filtering action of the pulmonary capillaries, were present in the lungs (Fig. 3), and a few were also present in the capillaries of the glomerular tufts. However, there was no destructive or exudative reaction around the glomeruli.

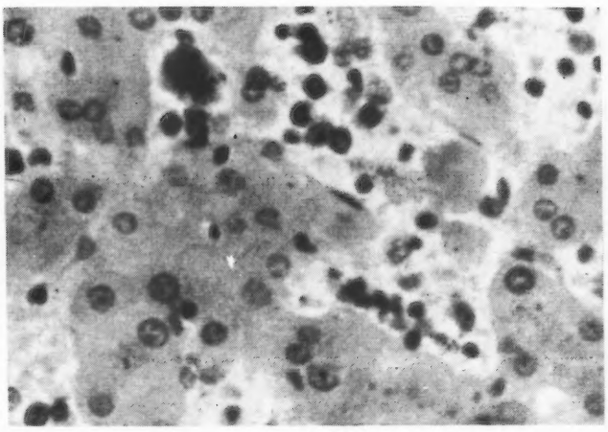

Fig. 2.—Hemopoiesis in the hepatic sinusoids.

Microscopic sections of the lungs demonstrated the presence of mixed, laminated thrombi in a number of the smaller pulmonary veins, which did not usually occupy the full lumen of the vein; there were no areas of infarction associated with them.

DISCUSSION

The myeloproliferative disorders include, in addition to polycythemia vera and the granulocytic leukemias, a number of conditions whose essential relationship has been obscured by the variety of names applied to them. Such terms as aleukemic myelosis, myelosclerosis with agnogenic myeloid metaplasia, leukanemia, leukoerythroblastic anemia, myelofibrosis, refractory anemia with hyperplastic bone marrow and many others are found in the literature. This renders any attempt to create an orderly classification of these conditions a difficult and time-consuming task. When it is realized that many of the disorders described under these names are either identical or closely related, the difficulty of clarification becomes obvious.

The current tendency, in the words of Dameshek and Gunz,[1] is to "synthesize these terms into one which would describe a single, definite syndrome and *to distinguish this from leukemia*, for many observers came to regard the two conditions as fundamentally different". Various observers might

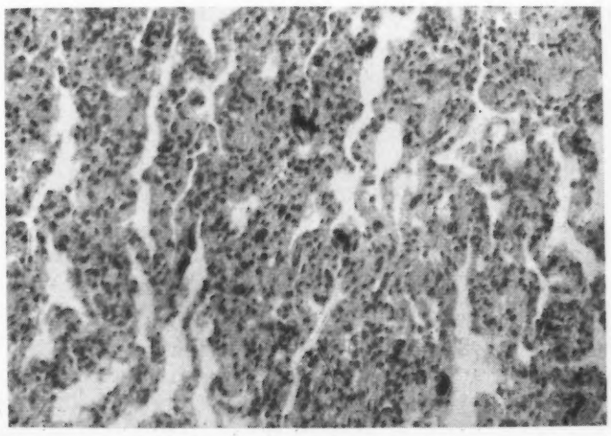

Fig. 3.—Megakaryocytes in a partially collapsed section of lung.

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differ as to the strength of this distinction, and the granulocytic leukemias remain disturbingly and uncomfortably close in their relation to this ill-defined group.

In the present case, to avoid the ungainliness of a fully descriptive name or the risk of inaccuracy of shorter names, the term "myeloproliferative anemia" is used. The characteristic pathologic feature of this disease, the presence of myeloid tissue in the spleen, liver and sometimes other organs, was once regarded as a purely compensatory response to the sclerosis of the marrow which so often accompanied it, even though it was an inefficient one. An increasing number of cases have been reported in which the marrow was frankly hyperplastic, and this helped to dispel this mechanistic concept. It was recognized that myeloid metaplasia was a general proliferation of marrow tissue in its normal intra-osseous position and in various ectopic sites. Hyperplasia of the bone marrow in this condition is now regarded as the early stage of a process which leads ultimately to fibrosis and sclerosis.

Venous thrombosis in various areas is a frequent complication of polycythemia vera; the greatly increased blood viscosity is commonly credited with this predisposition to thrombosis, but a greatly increased platelet count is frequently found also. One of the major difficulties in classifying the myeloproliferative disorders is this tendency for more than one constituent of the marrow to proliferate at the same time or at different times.

The case described in this report showed a decrease in the number of red blood cells, but there was still a marked tendency to thrombosis, as seen in the portal vein and in small veins of the lung. It is unlikely that the marked megakaryocyte hyperplasia in the bone marrow (Fig. 4) and elsewhere, and the many deviant platelet forms entering the peripheral circulation did not contribute to the tendency to thrombosis.

The contribution of the increased numbers of platelets should also be considered. On the only occasion when direct platelet counts were done, the results were within the textbook limit of normal for the method, but rather higher than the range, 150,000 to 250,000, usually reported by this laboratory. When the patient was in a terminal state, platelets were plentiful in the direct smear, but platelet counts were not done.

A platelet count higher than normal is the rule, rather than the exception, in the myeloproliferative disorders. In their series of 56 patients suffering from "agnogenic myeloid metaplasia", Linman and Bethell[2] found that platelets were slightly, moderately or markedly increased in 30. In other series or individual case reports[3-5] either qualitative or quantitative platelet anomalies are described. Because thrombosis is one of the dangerous consequences of an increase in platelet count following splenectomy, and because there is evidence of increased platelet counts during the thrombosis which

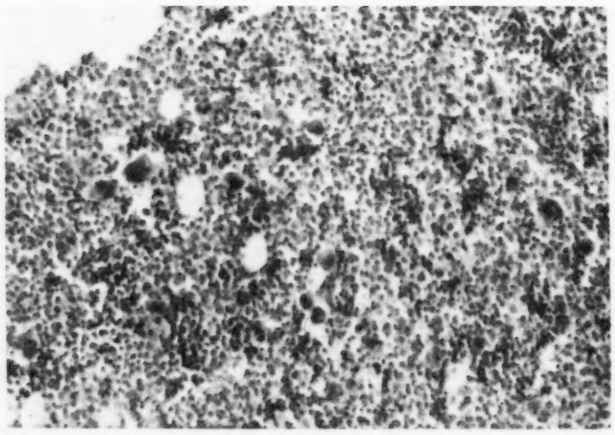

Fig. 4.—Sections of sternal marrow showing its cellularity and the megakaryocyte hyperplasia. The small cells are predominantly granulocytes and their precursors.

occurs following surgery or parturition,[6] it is clear that the conglutination of platelets is an important mechanism of intravascular thrombosis, perhaps as important as some of the better known disturbances of the coagulation mechanism.

In the case under discussion, the condition of the peripheral blood resembles that of polycythemia vera without its increased red cell mass and the increased blood viscosity. It is suggested, therefore, that the thrombotic tendency observed in polycythemia vera may be related not solely to the increased cell volume of that disease, but rather to the platelet disturbances which accompany it. The converse of the present case would be a case of polycythemia vera in which there was a demonstrable tendency to thrombosis, but an absence of any qualitative or quantitative abnormality of the platelets or their precursors, the megakaryocytes.

SUMMARY

A case is presented of a myeloproliferative anemia complicated by portal vein thrombosis and with evidence of a more generalized tendency to thrombosis.

It is suggested that the platelet disturbances in myeloproliferative disorders may be responsible for thrombotic incidents in this group of diseases.

We are indebted to Dr. Angus J. Neary, F.R.C.S.[C], who supplied the clinical data on this case.

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CULLEN'S SIGN IN RUPTURED ECTOPIC PREGNANCY*

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THE APPEARANCE of ecchymosis at the umbilicus as a sign of intraperitoneal hemorrhage is sufficiently rare to merit reporting, only 60 cases having been described in the literature to date. Eastman[1] recorded that he had seen only three cases, and in none of them was the discoloration sufficiently intense to be photographed.

The literature dealing with this sign has been admirably reviewed by Merrill,[2] who describes in detail the histopathology of this condition and discusses the theories of its formation. He points out that, although Cullen first described the sign in 1918 and labelled it "a new sign in ruptured extrauterine pregnancy", discoloration of the umbilicus due to the presence of peritoneal extravasations had been previously reported by Ransohoff in 1906. This author described jaundice of the umbilicus in a patient with a ruptured common bile duct, and in 1909, Hofstatter observed a blue discoloration of an umbilical hernia (Hofstatter's sign) in a patient with a ruptured tubal gestation. However, the discoloration in Hofstatter's case was not due to ecchymosis but rather to transmission of the colour of the blood through the thinned-out semi-transparent hernia. Excluding seven cases of Hofstatter's sign and two cases of Grey-Turner's sign (discoloration in the flanks and periumbilical area due to subcutaneous extravasation of fluid secondary to the digestive action of trypsin and lipase), Merrill found records of 57 cases of Cullen's sign in the literature and reported three additional cases, bringing the total to 60. Of these, 33 were due to ruptured tubal gestation, and the remainder were encountered in such varied conditions as acute pancreatitis, ruptured uterus, hematoma of the rectus sheath, ovarian cyst, pyosalpinx, rupture of the kidney due to malignancy, rupture of the liver due to malignancy, ovarian infarcts, abscess in the broad ligament due to infection occurring after abortion, hemorrhage from the liver and stomach due to gunshot wound, and peritonitis due to a ruptured appendix. In two of these cases (abscess in the broad ligament and ruptured appendix) no intraperitoneal bleeding was found. The discoloration has not been limited to the umbilicus, but in some cases has been observed in the midline below the umbilicus and in surgical scars elsewhere in the lower abdomen.

Mrs. D.L., a 36-year-old woman, was pregnant for the third time and has two living children; she had her last menstrual period on May 20, 1960. On June 19 she noted some spotting. On July 11, while travelling abroad, she had an episode of abdominal pain associated with fainting, vomiting, and involuntary micturition. The patient consulted a doctor in Dublin, who made the diagnosis of "colic". The following day her symptoms were slightly improved, and for the next two days she was free of pain. This patient returned to Canada, and on July 15 she began to have vaginal bleeding which she considered to be a normal menstrual period; she noted some discoloration of the umbilicus. At the same time the pain recurred and became gradually worse. On July 19 she consulted one of us (F.C.M.), who diagnosed a ruptured ectopic pregnancy, primarily because of the finding of Cullen's sign, and referred her for surgical treatment.

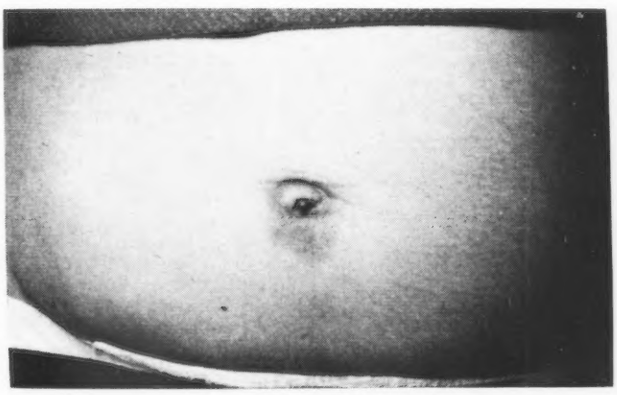

Fig. 1

On examination, the vital signs were normal and the patient appeared to be in no acute distress. The umbilicus was a reddish-purple colour, with an area of bluish discoloration around it and extending about 3 cm. inferiorly. There was generalized lower abdominal tenderness, more acute on the right, with some slight tenderness in the upper abdomen. On pelvic examination the uterus was the size of a two-month pregnancy; no adnexal masses could be palpated but the whole pelvis was tender and movement of the cervix caused acute tenderness, more marked on the right. The examination was repeated under anesthesia, and still failed to reveal any palpable masses.

At laparotomy fresh blood and old blood and blood clots were found; a tubal pregnancy arose from the distal end of the right fallopian tube. In the lower portion of the omentum old adherent blood clots were found. A resection of the distal end of the tube was performed; and the postoperative course was uneventful. The accompanying photograph (Fig. 1) was taken on the second postoperative day. The discoloration gradually faded and disappeared completely within a week.

DISCUSSION

The appearance of periumbilical ecchymosis is a rare observation, and when present, it is a late manifestation of intraperitoneal hemorrhage. In the present case, the discoloration was first seen by the patient four days after the onset of her first symptoms, and was first noted by a medical observer eight days after the onset of pain. In Cullen's case the discoloration began one week after the onset of pain. Undoubtedly prompt surgical treatment prevents the development of the sign in a great

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many cases. It is possible that in some cases the sign appears after operation without being observed. One also wonders how many patients with tubal abortion, who undergo spontaneous resolution without operation, may develop the sign and never come under medical observation. The degree of discoloration, or its presence, does not seem to be related to the amount of bleeding but rather to its duration and to other as yet undetermined factors.

Since the diagnosis of extrauterine pregnancy is beset with many pitfalls, including the fact that no mass can be felt in up to 50% of cases, the sign may be an important aid to diagnosis.

SUMMARY

A case of Cullen's sign occurring in a patient with an eight-day history of ruptured tubal pregnancy has been presented, together with a brief review of the literature. This case report brings the total number of cases in the literature to 61.

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SHORT COMMUNICATION

PHOTOGRAPHIC ILLUSTRATION FOR MEDICAL WRITING:*

III. MARKING, SPOTTING AND MOUNTING PHOTOGRAPHS FOR PUBLICATION

DONALD J. CURRIE, M.D. and ARTHUR SMIALOWSKI,
Toronto

THE PHOTOGRAPHIC print for publication may be marked for identification or for the purpose of directing attention to special features. The marks may be identification numbers or letters or other marks such as arrows and lines. Marks should be correctly placed, of uniform size, attractive in appearance and of sufficient contrast that they can be easily seen. They must be carefully fixed so that they will not loosen and become moved or lost, and they must be protected so that they will not be smudged. Neat and uniform lettering will enhance the overall appearance of an illustration.

Markings may be made by the author, photographer, artist or publisher. The most simple method of attractively marking photographic prints is by the use of commercial ready-made transfers. These transfers are available in a variety of sizes and forms of letters, numbers, lines, arrows and other standard figures. Marks may be carefully drawn on the face of the print by those who have sufficient ability in draughtsmanship.

Marks may be incorporated in a photographic print in a number of ways by an experienced photographer. If the author feels that he is not able to add the desired markings attractively or if he is unable to obtain the services of an experienced photographer, he may request his publisher to add marks for him. In this instance the author will have to provide his publisher with detailed instructions.

TRANSFERS

Transfers are available in letters, numbers, lines, arrows and other standard figures which may be applied to the face of a print. This is the safest method of marking a print, as the transfer can be removed or adjusted without damage to the surface of the photograph. It is also the simplest and most attractive method and may be used by anyone, with care. The transfer must be fixed firmly, and protected to prevent dislodgment. A variety of sizes and types of numbers, letters, arrows and lines are commercially available (e.g. "Zip-a-Tone", "Artype"). These marks are printed on transparent sheets which have an adhesive backing. The mark is cut out and fixed by pressure to the surface of the photograph.

If a commercially made transfer is not available, a transfer can be prepared by carefully cutting the desired figure from a calendar or other quality printed page. The figure is carefully cut out at its edges and pasted to the surface of the print with rubber cement or with water-soluble mucilage, which has the advantage that excess glue can be carefully washed away and the edges of the transfer can be spotted to blend with the immediate area of the photograph with water-soluble spotting ink ("Spotone"). If identification numbers or letters are correctly placed and other marks are used with discretion, the finished illustration will be attractive.

*From the Departments of Surgery and Photography, St. Michael's Hospital, Toronto.
This is the third in a series of five communications which are being published in successive issues.

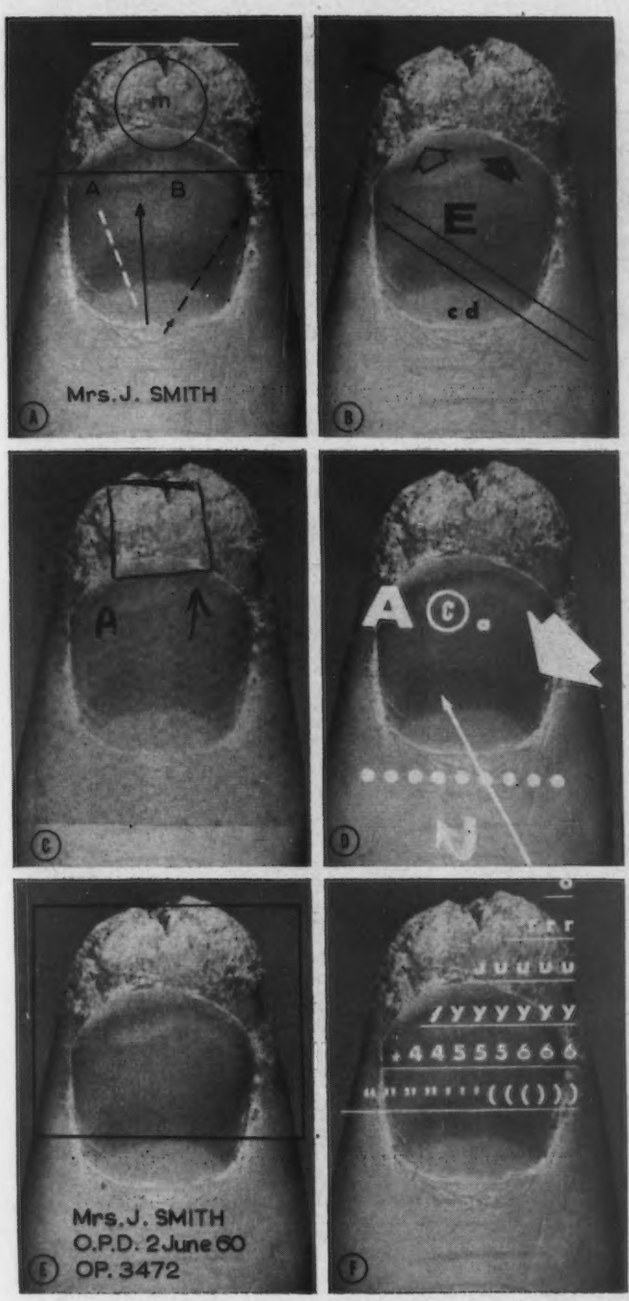

Fig. 1.—Examples of marks added to photographs for publication. (A) White and black India ink were used in drawing with rule and lettering guide on the surface of the print. (B) Commercially available transfers (Zip-a-Tone) were fixed by pressure to the surface of the photograph. (C) Instructions for marking a print may be drawn on a transparent overlay and the marks are added by the engraver. (D) Photographic method may be used in which two sandwiched negatives are printed simultaneously. (E) Negatives were prepared of the subject and of a line drawing. The two negatives were printed one after the other on the same photographic paper. (F) The print was made with a triangular piece of transparent sheet of transfers on the enlarging paper. The photograph shows a large recurrent common wart on the tip of the thumb.

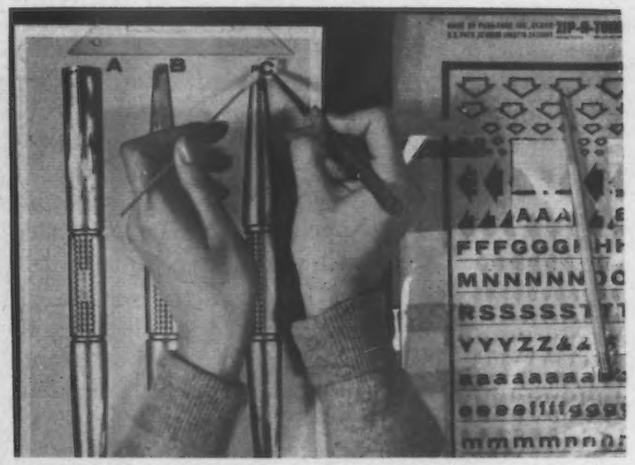

Fig. 2.—The simplest, safest and most attractive method of marking photographic prints is by using commercially made self-adhesive transfers. A selection of transfers, scissors, transparent ruler, and tweezers are the only tools required.

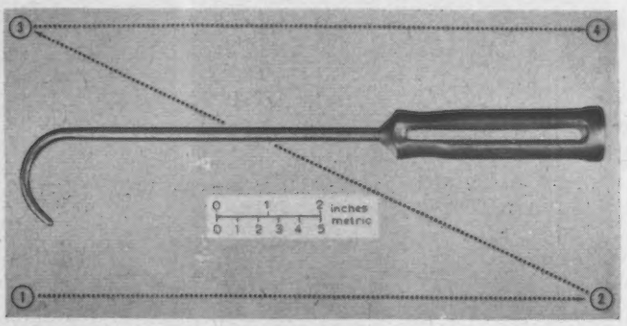

Fig. 3.—Correct placement of identification numbers and letters. Identification figures are placed in the corners of illustrations. This illustration shows the order of preference for placing the identification numbers or letters; the lower left corner is preferred. A little space should be left between the edge of the figure and the borders of the illustration.

INK DRAWING

Illustrations may be labelled by carefully drawing on the photograph with black or white waterproof India ink, by anyone who has sufficient ability in this type of art work. The only available print must not be marked by ink drawing, because the ink may smudge or the photograph may be incorrectly marked and ruined by the permanent ink marks. It is difficult to draw on a glossy emulsion surface. The dried ink mark is easily cracked or chipped. Marking with ink should be used only where a duplicate print is available or can be made. Even though lettering guides are used, the same person should mark all photographs in a publication to maintain the same style. The special pen used by draughtsmen should be used in drawing straight lines in ink. Black drawing ink is easier to apply, but white ink is necessary in marking dark areas. In areas which are both light and dark, both black and white inks may have to be used. Marking photographs in ink is a very satisfactory method for those with experience.

PHOTOGRAPHIC METHODS

Markings may be added to a photograph during the process of printing by the use of two negatives. The negative of the subject is exposed first and, without moving the photographic paper, the subject negative is replaced by a second negative made from a line drawing of the markings. A second exposure is made. The print will show the photograph with a superimposed image of the line drawing in black.

A white mark such as a cutout of an arrow may be added to a photograph during enlarging if it

is carefully placed on the enlarging paper to block light from the area of the cutout.

White markings may be added to the photograph by printing simultaneously a sandwiched positive transparency with the original negative. By this method, a line drawing in white can be added very attractively. These photographic methods can be used only by an experienced photographer, as the techniques are complicated.

The author who does not have the services or ability to add markings attractively to photographs may ask his publisher to do this work for him. The author should record his detailed instructions for the desired markings on translucent tissue paper fixed on the face of the print.

The marking of photographs for publication may be simple or complex depending upon the nature of the photograph, the result desired and the method employed.

SPOTTING

Spotting is the technique of removing or blending small imperfections in a print or negative. Most prints, in spite of careful handling, will have blemishes caused by dust, scratches, finger marks or other causes.

The tools required for spotting are simple and consist of fine artist's brushes, an etching knife and spotting ink ("Spotone"). Most photographs used for publication are glossy prints. The glossy surface is more difficult to spot than the matte surface. White blemishes on glossy prints are blended to a suitable grey tone with spotting ink. Using a fine brush, spotting ink is diluted with water on a palette or dish until the desired tone is reached. Before spotting the print, the diluted ink should be tested on white paper. The white blemish is painted until it becomes invisible. This is a simple method which can be used by either the photographer or the author. Spotting inks may be used to subdue highlights or to darken small areas to increase contrast. To remove black blemishes it is necessary first to change the black blemish to white by etching the print or by spotting the negative and reprinting. The white blemishes on the print are then spotted with spotting ink. Pencils should not be used for spotting glossy prints.

ON MOUNTING PHOTOGRAPHS

Photographs submitted for publication should not be mounted. The publisher may wish to unmount photographs for grouping or cutting and there is great risk of damage to a photograph in unmounting. Mounting is used where photographs are exhibited or where prints will be handled by a number of people.

In submitting prints for publication, photographs should be protected by cardboard. In preference to permanent mounting of photographs it is better to attach the prints lightly to oversized sheets of firm cardboard, by tape at the corners. Glues, cements and other adhesives can damage prints if not used properly and sparingly.

Most photographic prints have some minor imperfections which can be eliminated by spotting. Prints may be marked for identification or for indication of their important features. Photographic prints should be protected by cardboard stiffeners. A little extra effort and care in preparing photographic prints will be rewarded by more attractive and valuable illustrations when published.

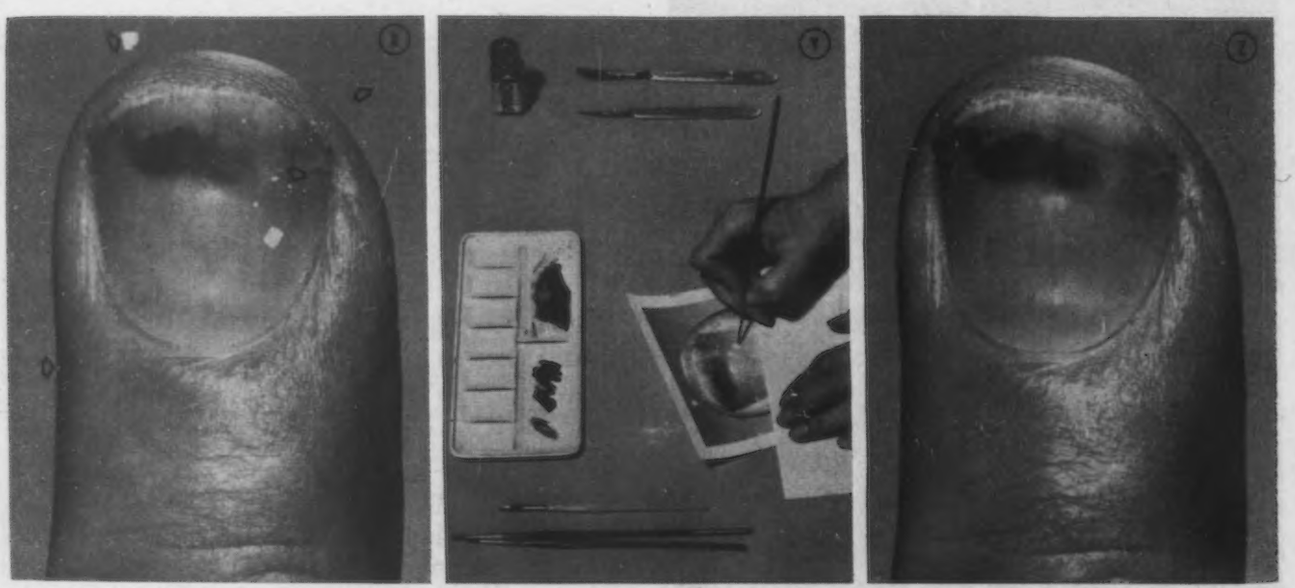

Fig. 4.—Subungual hemorrhage following the destruction of tumour (oncolysis). The time and care spent in careful spotting greatly improve the appearance of the photograph. Arrows point out some of the blemishes in photograph X. The appearance of the print after careful spotting is shown in Z. Small black spots are removed by scraping. All white blemishes are then blended with their surroundings by various concentrations of spotting ink applied by fine brushes.

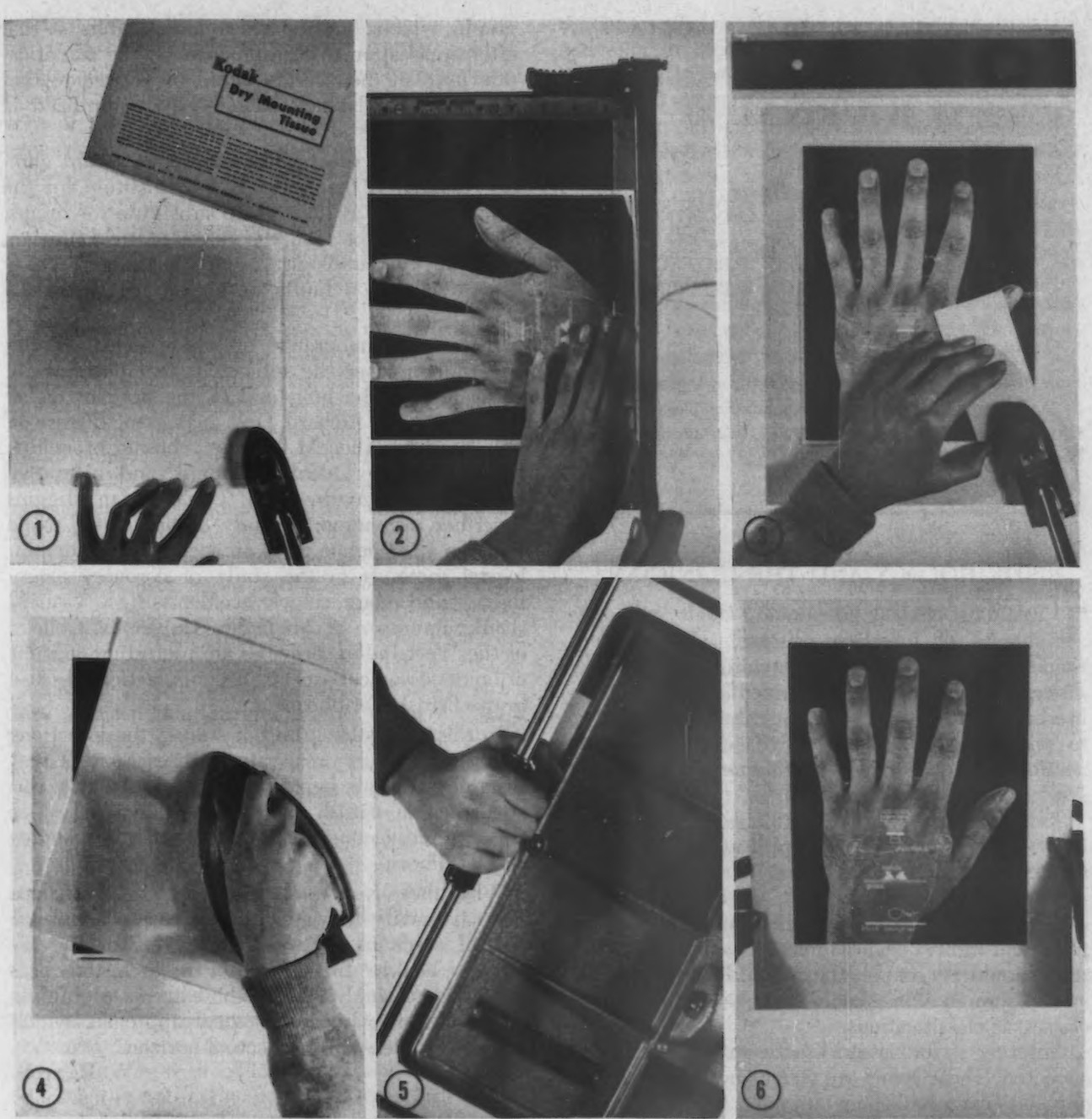

Fig. 5.—Dry mounting of photographs. 1. Dry mounting tissue is stuck to the back of the print by heat. 2. The print and mounting tissue are neatly trimmed. 3. The photograph is stuck at the corners to the cardboard mount by a tacking iron. 4. The whole print is fixed to the mount by pressure and heat with a household iron, or with 5. a dry mounting press. 6. The cardboard mount is trimmed if necessary. Dry mounting is a good method of permanently mounting photographic prints.

PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

Physiological albuminuria having been definitely accepted, it is obvious that those individuals exhibiting this phenomenon ought not to be excluded from the advantages of life assurance, or from entering the services, or from clerkships in banks and other public and private offices. But a very real difficulty lies in recognizing the true state of affairs, and unless each case is watched for some time and frequent examinations of the urine are made, the medical adviser to an insurance company naturally hesitates to accept an individual for insurance at ordinary rates if albumin has ever been detected in the urine. The occurrence of albumin in athletes or in those who have undergone a prolonged strain in preparing for examinations does not as a rule present such difficulties. Rest from exacting muscular effort, a holiday, and relaxation of severe mental effort will probably have the desired effect in freeing the urine from albumin and indicating its transitory appearance. Unless such precautions are taken, a too hasty conclusion may be formed as to the presence of structural disease of the kidneys, and so undue interference with a career or a method of living may be inflicted and unnecessary anxiety may be caused.—*The Lancet;* quoted in *Canad. M. A. J.*, 1: 902, 1911.

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EPIDEMIOLOGY AND THE CLINICIAN

TRADITIONAL epidemiology dealt with epidemics of infectious disease, while modern epidemiology studies group manifestations of any disease. But, in addition, epidemiologic methods are being applied not only to clinical medicine but to clinical trials and operative research in connection with the need, or otherwise, for health services and developments.

As epidemiology is greatly involved in measurement, one of its important applications in clinical medicine is the determination of observer error. As Fletcher[1] has pointed out, all indices used in clinical disease should be defined with the greatest precision. Indices of measurements should be valid; they should be simple; they should be repeatable, and discrimination should be possible between classes or classifications.

Observer error is not sufficiently stressed or accepted. These errors are serious not only because of their magnitude but because of the curious resistance of physicians to the idea that they do exist at all. In relation to error in the reading of chest films, Newell *et al.*[2] say: "In discussing this research with others, radiologists and chest specialists, the writers find a general unwillingness to believe that descriptions of pulmonary lesions are as unreliable as were found in the present study. The present writers have become accustomed to this scepticism and believe that only those who have themselves made duplicate readings of a series of films can come to appreciate the hard fact of their own unreliability."

The literature of medical surveys is often frustrating because of failure to attend to the precision of definitions and to the influence of observer error which destroys the value of the results. There would seem to be a need for some sort of international bureau which might hold series of films, electrocardiographs and perhaps clinical photographs, which could be lent to investigators, so that after application to the standard set the classification used in their series would be related to that of other series which have been standardized in the same way.

The crux of successful epidemiologic and clinical research is that there is no substitute for the good clinician, as there is no substitute for brains. Machines cannot take the place of the clinician. And the epidemiologist cannot adequately study disease based on faulty or inadequate diagnostic acumen.

A recent monograph[3] on epidemiology shows the wide field of the subject. It includes a study on cancer of the lung and of the nose in nickel refiners by W. Richard Doll, malignant disease in childhood by Alice M. Stewart, chronic bronchitis in postmen by Donald D. Reid, and ulcerative colitis in Norway by H. J. Ustvedt. Ian Higgins describes a community study of bronchitis, while Herman E. Hilleboe gives an account of epidemiological methods in the study of coronary artery disease and motor vehicle accidents. E. K. Cruickshank, Professor of Medicine, University College of the West Indies, provides an interesting account of epidemiological aspects of non-infectious disease in the British Caribbean.

In this particular group of studies the infections dealt with were respiratory disease in Great Britain, infectious hepatitis in Czechoslovakia and gonorrhea in British Columbia, while the rest of the account of non-infectious diseases also includes mental illness.

What these trends all clearly show is that there is no boundary between preventive medicine and clinical medicine, between public health and individual health.[4] In the field of research, the clinician is increasingly finding the extreme usefulness of the group or epidemiological approach, which markedly widens his intellectual horizon.

W. H. LE R.

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HEALTH EDUCATION OF THE PUBLIC IN CANADA

HEALTH, as defined by the Constitution of the World Health Organization, is "a state of complete physical, mental and social well-being, and not merely the absence of disease or infirmity". The aim and general purposes of health education of the public are delineated by the WHO Expert Committee on Health Education of the Public in

its first report (1954): "The aim of health education is to help people to achieve health by their actions and efforts. Health education begins therefore with the interest of people in the improvement of their conditions of living and aims at developing a sense of responsibility for their own health betterment as individuals and as members of families, communities or governments."[1]

No single individual or group of individuals is, or can be, responsible for the health education of the public. Doctors, medical associations, public health departments, schools, voluntary agencies devoted to the conquest of specific disease, or, in a few instances, to the promotion of general health, and commercial organizations all have a role to play in the dissemination of health information. The ways in which health education may be carried out are many: by person-to-person communication, by example, by teaching in the schools, by dissemination of communications from medical associations and health agencies through the mass media of communication—the press, magazines, exhibits, lectures, radio and television, and health forums, and by the creation of health museums.[2]

Of all the techniques of health education, the doctor-patient contact is the most important. In Canada we recognize that it is inherent in a doctor's duty to his patient to give advice about healthful living.[3] Most practitioners attempt to fulfil this duty, to a greater or lesser extent, since they realize that their chances of therapeutic success are better with an educated, intelligent, co-operating patient than with one who merely gives blind obedience and unquestioning faith. The extent to which a practitioner attempts to educate his patients depends on many factors, including his own personality, the role of the doctor as perceived in the sub-cultural group in which he was raised, the philosophy of his medical school, the precepts and examples of his teachers in medical school, and the pressures of other tasks which claim a higher priority.[4] But, as with education of any type, health education is not just a "one-way" street; the public must meet those attempting to educate them at least part-way: to succeed, health education must be accepted willingly by a public which is interested in and which wants to improve its health.

In Canada there are many organized efforts directed to health education of the public. The Canadian Medical Association, through its Department of Public Relations, endeavours to co-operate with and work through all of the mass media for this purpose, and has generally become accepted as a source of guidance in the preparation of news stories. The scientific papers presented at the Annual Meeting of the Association and the articles appearing weekly in the Journal provide ample material for health messages. The Canadian Medical Association does not publish a popular magazine on health, but this void is ably filled by the Health League of Canada through its magazine, *Health*. The Association also assists the efforts of the many official and voluntary agencies which are active in promoting education in their respective fields of interest by helping to enlist the services of medical experts for their boards and by endorsing and supporting their health messages. Currently, the Association itself is producing T.V. filmettes (60-second messages designed for repeated showing by co-operative television stations) dealing with such topics as obesity, accidental poisoning in children, and physical fitness. Experiments have also been tried with health forums in which a panel of physicians discuss in appropriate terms a specific area of health or disability before as large a lay audience as can be attracted.

One very successful activity of the Ontario Division of the Canadian Medical Association is worthy of special mention, namely, its mammoth health fair, "Mediscope". This fair, first presented in 1959 and presented again at the Canadian National Exhibition in 1961, consists of very attractive displays devoted to a wide variety of subjects in the field of health and disease. Each display is attended by relays of physicians prepared to explain and amplify the messages portrayed.

Although, as stated previously, the physician's chances of success in treating his patients are greater with an educated co-operative patient, it is not to be lightly assumed that the education of the public in health matters is a simple task, a matter of a few words and/or a few pictures. First, the public must be interested in health, and then they can be taught. Prudence must be constantly exercised in providing the public with such information; health education may readily be overdone, and appeals based on fear and alarm may readily result in emotional responses that are harmful to patients and which, far from making the physician's work easier and more successful, only add to his problems. F.L.

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NUTRITIONAL FACTORS IN TOOTH FORMATION AND DENTAL CARIES

FACTORS controlling tooth decay operate through the oral environment and through systemic pathways during tooth development. Precise knowledge of the role of the various causative factors has not yet been obtained, but it is felt that bacteria are a necessary ingredient, since caries-susceptible rats maintained under germ-free circumstances never develop carious lesions.[1, 2] Unfortunately, relatively little is known about the identity of the causative micro-organisms. Besides bacteria, another factor operating through the oral environment is the nutritional substrate available

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to the micro-organisms. In this regard, carbohydrates are mandatory for the metabolism of caries-producing oral flora. Without carbohydrate in the restricted areas where bacteria cause tooth decay, carious lesions do not occur.

Nutritional factors operate also through systemic pathways, during dental calcification and maturation, to alter caries incidence. Although genetic inheritance is probably the most important determinant of dentition, recent attempts to vary developmental environment through nutrition, and the effect of these variations on developing teeth in terms of tooth morphology and caries susceptibility, are worthy of note. It has been shown that the shape of teeth is related to susceptibility to dental caries in both humans and experimental animals. Further, abnormal variations in tooth form in animals can be produced experimentally by altering the developmental environment of the teeth through nutrition. Paynter and Grainger,[3] of Toronto, have demonstrated in rats that in the offspring of mothers fed a high phosphorus-calcium ratio diet, the teeth were smaller and had morphologically altered fissures, and a marked increase in caries. Use of a low protein, high carbohydrate diet during the period of the rat's tooth development was found to reduce tooth size and increase caries susceptibility. However, smaller teeth are not related directly to caries susceptibility, since vitamin A deficiency produces smaller teeth in the offspring but does not affect caries susceptibility.

The relation in humans between tooth size and caries susceptibility is not clear. In an Ontario community in which fluoride was naturally present in the water supply, more pit and fissure caries tended to develop in the larger teeth. This apparently greater caries susceptibility of larger teeth has not been explained.

A number of discrete chemical agents influence the incidence and severity of experimental caries in the rat and hamster.[4] Some of these agents have been clinically tested in the human.[5] As reported by Zipkin,[4] various fluorides (sodium fluoride, sodium silicofluoride, sodium phosphorofluoridate, ammonium silicofluoride, and stannous fluoride, given posteruptively), sodium lauroyl sarcosinate (SLS), lysine, various phosphates, penicillin and tetracycline have been found to reduce caries activity in experimental animals. Ethylenediamine tetra-acetic acid (EDTA) and dehydroacetic acid (DHA) potentiate caries activity. In general, trace elements and vitamins have not been found to play any significant role.

Striking correlations occur between areas on the teeth where decay originates and those from which food deposits are removed least rapidly. These emphasize the role of local as opposed to systemic factors of nutrition and general health in the causation of caries. For example, caries is 600 times more frequent on the occlusal surface of the molar than on the lingual surface of the lower incisor. The explanation of this phenomenon is that the occlusal surface of the molar is ideally situated for food retention, whereas the cleansing effect of tongue movements and salivary flow on the lingual surface of the lower incisor prevent food retention at that site.

As might be expected, except for highly retentive foods, the total caries attack on a tooth surface is related more closely to the frequency with which carbohydrates enter the mouth than to the total amount consumed. In one study cited by Bibby,[6] bread containing 50 grams of sugar eaten once a day produced no caries increase, but when this amount was distributed over four meals, a definite increase of caries resulted.

In general, increased sugar consumption produces an increase of caries; sugar in liquid form is less cariogenic than sugar contained in a carrier such as bread; and the more frequently sugar is eaten between meals, the greater the increase in caries.

Attempts are now being made to find tasty foodstuffs of low cariogenicity or with protective properties that can be substituted for cariogenic foods. So far, a number of factors in unrefined foods and possibly milk have been found to offer some protection to the teeth against decalcification.

These rapidly expanding areas of investigation of dental caries offer considerable promise of further significant advances in dental health in the near future.

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PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

The discovery of the circulation of the blood by Harvey in 1616 affords an illustration of the reluctance on the part of scientists at that period to accept revolutionary ideas. If one reads the account of Harvey's experiments, one cannot help being impressed by the thoroughness of his demonstration and of the logical deductions he made therefrom. Although the existence of capillary blood vessels was not proved until nearly half a century later, when Malpighi (1661) demonstrated their presence by means of a magnifying glass, yet Harvey's demonstration without this missing link was most convincing. Here, again, it was the slavish regard for the authority of Galen and Hippocrates which proved the stumbling block to the acceptance of Harvey's views. For thirty years and more he struggled to convince his colleagues, and though he gained an increasing number of converts to his views, many of the authorities of the day refused to abandon the doctrine of the ancients.—A. Primrose: Address in Surgery, *Canad. M. A. J.*, 1: 603, 1911.

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Letters to the Journal

ANTI-INFLAMMATORY EFFECT OF OXYPHENBUTAZONE

To the Editor:

The August 5 issue (*Canad. M. A. J.*, 85: 295, 1961) contained a preliminary report by Dr. W. Dennis Fraser *et al.* on the anti-inflammatory effect of oxyphenbutazone in postoperative obstetric and gynecological practice. I started reading the report with a great deal of interest but was disappointed by the lack of certain essential data.

It is stated that "the data were summarized and transferred to punch cards". Just what was recorded?

The report gives four tables showing the degree of "response" to drug therapy as compared with placebo. The report fails to mention how this "response" was measured.

The report states that the "response" consisted of a reduction in pain and swelling and that the pain response was not very good unless treatment was continued for three days. Apparently this effect "was observed in the reduction of the number of patients requesting specific analgesic drugs". Since the response to oxyphenbutazone was "complete" or "marked" in 89.1%, while the response to *placebo* was "complete" or "marked" in 72%, the results do not justify the conclusion that "pain and swelling were markedly reduced in those patients on oxyphenbutazone therapy".

How significant was the reduction of swelling? The authors do not indicate how swelling was measured or evaluated, and it should be clarified how one can measure reduction of swelling in terms of "complete", "marked" and "slight".

Possibly this report permits the conclusion that after three days of concentrated treatment, 1.7 out of 10 patients will have less pain or swelling than they might have had otherwise.

However, the report gives us no reason to expect that aspirin would not have worked just as well or better, inasmuch as it would do the same in less than three days. And I am sure that few patients would enjoy waiting for three days, hoping that they will belong to the fortunate 17% in whom the drug takes effect, when this could have been achieved within a few hours by other and safer medication in a far larger percentage.

WM. F. KREMER, M.D.

P.S.—I have one more question. How can a placebo cause stomatitis or ileus? W.F.K.

85 Jane Street,
Hartsdale, N.Y., U.S.A.

To the Editor:

It is always stimulating to find that there has been sufficient interest in an article to produce a letter to the editor, albeit one which is so strong in its criticism of the manner in which the report was made. Possibly the humour is subtle beyond our comprehension. We shall attempt to reply categorically, without humour.

The assessment of an anti-inflammatory drug must be based on the clinical findings of pain, swelling, and inflammatory reactions (erythema and/or redness). These must be carefully checked by the same individuals daily during the period of investigation (see headings of Table VIII) and on a "double-blind" basis to rule out prejudice.

Pain, as was noted under the heading "Assessment of the Patient", is obviously a difficult symptom to assess because of the reasons described. The symptom of pain was noted to be either severe, moderate, mild, or absent according to the patient's complaint and description of pain, and in the desire of each patient for other forms of analgesia. As an example: it is more or less a routine order to prescribe a potent analgesic after a major abdominal or vaginal operation. In our pavilion almost 90% of patients are given Dilaudid 1/32 grain or 1/16 grain postoperatively every four hours for 24 hours. The usual number of doses required is from two to six in the first 36 hours. This order is followed by two tablets of APC & C (codeine ½ grain) every four hours as required, the average number of tablets given varying from four to six in the ensuing 36 hours. It was felt by the investigators that, if the patient had complaints of pain and required only one or two injections of Dilaudid or an analgesic of similar potency in three days, there was marked pain relief. This also holds for medication with APC & C tablets. Increasing complaints of pain, and desire for other analgesics, changed that patient's category from marked relief, to moderate relief, to no relief. It must be noted, as in other series describing relief of pain, that there were 46 patients given placebo who described no pain.

The edematous reaction around wounds was best noted in episiotomies where inspection of the wound was made daily. The edema and erythema of perineal wounds are much more than that observed in abdominal wounds. It is our practice to have the perineal wound uncovered, and abdominal wound dressings changed on the third postoperative day and daily as required thereafter. Where edema was present, it was measured as to extent under sterile precautions, by the gloved hand, and an estimate of size of reaction made in centimetres. Erythema, where present, was measured in area with centimetre rulers. (It should also be added that fully 95% of the episiotomies in this series were mediolateral.)

The information gathered regarding redness, swelling, and pain was then entered on a daily patient sheet; the response was charted as complete, marked, slight, or no effect, and tabulated together with day of response, type of procedure, age, dosage, duration of treatment, and side effects: the information was then transferred to a standard punch card.

Please note, under "Discussion", that "the drug is effective only after a loading dose and three further days of therapy". We go on to make our point that such a regimen will not be acceptable to many physicians (indeed it may be unwelcome because of more serious side effects, to wit, the seeming lack of localization of infection in a few patients!).

Quick reading may lead one to false assumptions. The full statement was: "The response to oxyphenbutazone was complete or marked in 89.1% while to the placebo was complete or marked in 72%, a difference noted to be *statistically* highly significant." A

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statistically significant result, however, may not mean a *clinically* significant one, since differences in patient response, although measurable, may be too slight to be of practical importance. Our conclusions are reported, and the decision of practicality must be left to the clinician.

We would be most interested to see the results of a double-blind study on pain and swelling with aspirin and a placebo, conducted by an investigator of Dr. Kremer's choice. We agree wholeheartedly that there are more effective methods to deal with pain, as our work has borne out.

The very conditions of a double-blind study highlight the pixie humour of Dr. Kremer's postscript, since we as investigators could not and did not know which patient was receiving the drug and which patient the placebo when gastritis, nausea and vomiting, stomatitis, ileus, and/or headache became part of the postoperative clinical picture. Obviously if Dr. Kremer persists in this question he must consult his pixies for an answer.

The questions asked in the body of Dr. Kremer's letter are legitimate questions of a critical reader. We believe we have demonstrated that the drug is effective in relieving pain and edema. As we have noted, the requirements of a loading dose and three days of therapy will not appeal to many physicians, who will want to relieve pain as rapidly as possible. Hazard may exist if the drug really does interfere with localization of infection. Possibly we may find on further study that the drug has a more important use in the control of phlebitis when other anticoagulants are contraindicated.

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P. J. BEARDALL, M.D. and
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MEDICAL NEWS IN BRIEF

ARGININE HYDROCHLORIDE AS AN ACIDIFYING AGENT

The effect of acidification on the diuretic action of various drugs, particularly the mercurials, by the induction of a hyperchloremic acidosis has been recognized for many years. Ammonium chloride has probably been the most widely used agent, but its use is inadvisable in patients with liver disease, since it may induce the syndrome of hepatocerebral intoxication. The effects of the intravenous administration of arginine hydrochloride on acid-base balance have been reported. This compound would appear to obviate the dangers of administration of ammonium precursors in the patient with liver disease and may actually contribute to lowering blood ammonia levels in such patients via stimulation of urea synthesis, or induction of acidosis. The study by Manning and Delp (*Am. J. M. Sc.*, 241: 575, 1961) was undertaken to determine the effectiveness of the oral administration of arginine hydrochloride as an acidifying agent in patients in whom ammonium salts or ammoniagenic materials might be toxic.

Thirty-one patients were given arginine hydrochloride by mouth. All patients who received 30 g. or more showed a drop in pH and a rise in serum chloride value within 48 hours. The induction of this hyperchloremic acidosis was associated with an augmented response to the administration of organic mercurial diuretics.

No patient developed hepatocerebral intoxication which could be directly attributed to the administration of organic mercurial diuretics. One patient developed a profound hyperchloremic acidosis which was irreversible and may have significantly contributed to his demise. No other toxic effects were noted, except occasional diarrhea which responded to reduction of dosage.

INADVERTENT PARATHYROIDECTOMY

The chance finding of parathyroid tissue in the surgical specimen of patients who have progressed uneventfully after thyroidectomy and the occurrence of tetany in patients whose operation specimens show no trace of parathyroid tissue make the paper of Murley and Peters in the *Proceedings of the Royal Society of Medicine* (54: 487, 1961) of special interest to many physicians. Since August 1, 1954, pathologists of the Royal Northern Hospital Group (London) have carried out a detailed search for parathyroid tissue in all thyroid specimens in order to determine (1) the incidence of inadvertent parathyroidectomy and (2) to examine the relationship of this to postoperative tetany.

Naked-eye identification of parathyroid tissue in the laboratory, though often easy, can be difficult. Approximately 70% of the parathyroids found have been identified in this way. In about 40% of specimens in which the pathologist suspected parathyroid tissue he failed to confirm it by microscopy. Classically yellowish or brownish, the parathyroids are sometimes concealed in fat, lymphoid tissue, thyroid, or even in contiguous thymus. Sequestered thyroid nodules, lymph nodes, fragments of congested fat and thymic remnants may all resemble parathyroids.

In the first five years of this investigation 332 thyroid specimens were examined, 46 of which included parathyroid tissue. Two parathyroid glands were present in five of the 46 specimens. The various case records are not sufficiently complete to allow the precise extent of the thyroid resection to be determined for the whole series. In the personal experience of one of the authors, parathyroid tissue was present in 9.9% of 142 cases: and other surgeons, unaware of the purpose of the study, had an incidence of 16.8%.

Inadvertent parathyroidectomy is much more common than is generally appreciated. The high incidence

in this series is better attributed to the zeal of the pathologists than to the clumsiness of the surgeons. Most of the subjects of inadvertent parathyroidectomy suffer no apparent tetany or other ill-effects from gland removal. Indeed, tetany often occurs in the absence of parathyroidectomy when it is usually transient and presumably due to bruising of the parathyroids. That tetany is more common after operations for toxic goitre is probably due to the greater vascularity of the thyroid and other local peculiarities in such cases.

The practical lesson to be learnt from this research is that, despite the exercise of considerable care at operation, inadvertent removal of parathyroids is not uncommon. It rarely causes serious trouble, but it is clearly a hazard which, together with rough handling of parathyroids, every surgeon should try to reduce to a minimum. Figures recently published by Painter (*Brit. J. Surg.*, 48: 291, 1960) add emphasis to the need for care: a 13% incidence of permanent tetany was recorded following 46 operations for toxic goitre.

REPRODUCIBILITY AND RELIABILITY OF THE SCHILLING TEST

Deficiency of vitamin B_{12} in man can occur from a variety of causes, the most common in temperate climates being diminished absorption from the alimentary tract. The capacity to absorb vitamin B_{12} can be estimated with any degree of accuracy only by use of the radioactive vitamin in absorption studies. These tests are of considerable assistance in defining the nature of the defect and are often the only means of establishment of diagnosis in patients who have received treatment. Of the methods used to investigate the absorption of radioactive vitamin B_{12}, the urinary excretion test, introduced by Schilling, is the most convenient and thus has found wide acceptance. Briefly, this test entails administration of an oral dose of radioactive vitamin B_{12} followed by an intramuscular injection of the nonradioactive vitamin; the greater part of the intramuscular dose is excreted in the urine and "carries out" some of the radioactive vitamin B_{12} which has been absorbed from the intestine. The amount of radioactivity in the urine over the next 24 hours thus gives an indication of the amount of the radioactive vitamin B_{12} absorbed from the intestine.

This test has been used extensively since its introduction in 1953, and, in general, individual experience has been in keeping with published results. On a few occasions, however, anomalous results are obtained which cannot be ascribed to technical errors; this applies particularly to tests used in a semiquantitative manner. Reference to the literature shows that little attention had been paid to the reproducibility of the test. For this reason Adams and Seaton (*J. Lab. & Clin. Med.*, 58: 67, 1961) carried out a study designed to yield information about the reproducibility and reliability of the test.

The reproducibility and reliability of the Schilling test in the same individual were assessed by a study involving repeated Schilling tests in seven patients with pernicious anemia, two patients who had undergone total gastrectomy, and one patient with adult celiac disease. The test was found to be reliable and reproducible in demonstrating malabsorption of Co^{58}-labelled vitamin B_{12} in patients with pernicious anemia and in those who had undergone a total gastrectomy; a wide range of results was obtained in the patient with celiac disease.

When Schilling tests were performed with intrinsic factor in the patients with pernicious anemia and in those who had undergone total gastrectomy, there was evidence that the effect differed not only from patient to patient but also in the same patient at different times. The test with intrinsic factor was not reliable unless the dose of the factor was adequate. Difficulties of determining an adequate dose of intrinsic factor are outlined and illustrated by the results. There appeared to be an absorption defect in patients who had undergone total gastrectomy which differs from that found in patients with pernicious anemia. Administration of oral calcium did not increase the absorption of vitamin B_{12} in the patient with celiac disease.

HEXADIMETHRINE BROMIDE (POLYBRENE), A NEW ANTICOAGULANT

Hexadimethrine bromide (Polybrene), a quaternary ammonium salt with the empirical formula $C_{13}\ H_{30}\ Br_2\ N_2)_x$, has been known to have an anti-heparin action since 1952; since then it has been reported to be an anticoagulant as well. Shanberge *et al.* (*J. Lab. & Clin. Med.*, 58: 23, 1961) carried out studies to determine its *in vitro* effect on the various stages of blood coagulation. In concentrations comparable to dosages administered clinically, hexadimethrine bromide prolongs whole blood clotting, probably by interfering with the production of "thromboplastic" activity, thus hindering conversion of prothrombin to thrombin. The degree of inhibition of coagulation achieved by hexadimethrine bromide is inversely related to the number of platelets present. In the thromboplastin generation test, its inhibition is also counteracted by heparin and serum factors, particularly prothrombin, factor IX, and, to a lesser extent, platelet-like activity of serum, but not by a crude cephalin or by adsorbed plasma.

Hexadimethrine bromide is fibrinoplastic in the thrombin-fibrinogen reaction, but does not itself precipitate fibrinogen from plasma. In relatively higher concentrations, it delays the one-stage prothrombin time determination and agglutinates erythrocytes.

The clinical implications of these findings are complex. For example, unlike heparin, hexadimethrine bromide is not antithrombic but, as with heparin, thrombocytopenic blood or plasma is more sensitive to the anticoagulant action of hexadimethrine bromide. Therefore, although the concentrations of hexadimethrine bromide required to influence normal blood coagulation *in vitro* are somewhat higher than those usually recommended in its clinical use as an antiheparin, its margin of safety as far as overdosage is concerned may be much less than that of protamine if the platelet count is lowered.

Hexadimethrine bromide could effect blood coagulation in a number of ways, but how specifically it does so is difficult to explain. It is a polyelectrolyte like heparin and protamine; it may act by either emulsification or neutralization of molecules. A clearer understanding of how these substances exert their actions on blood may provide further clues to the mechanism of blood coagulation itself.

(Continued on advertising page 29)

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THE LONDON LETTER

THE LOST TOOL OF LEARNING

The inability of the medical profession to express itself in plain English has long been a source of wonder to the laity. But the lay concern is mainly with technical jargon for simple things (the best example this writer knows is that of the soldier who appeared a day late from Christmas leave waving a doctor's certificate with a diagnosis of "cephalgia"), whereas there is a far deeper concern in medical educational circles with the growing inability to make plain statements even in jargon. Modest North Americans are often under the misapprehension that this state of affairs does not obtain in Europe, but they can take comfort from an address given this summer by Sir George Pickering, and entitled "Language: the lost tool of learning in medicine and science". The speaker said that the function of language was to convey information accurately and from one mind to another, and then gave examples to show how it was being used to obscure simple issues. Much of his thesis was concerned with the incorrect or unnecessary use of jargon (he pointed out that the word "atherosclerosis" literally meant "hard porridge"), but he also drew attention to the abominably low standard of composition, verging on illiteracy, which all examiners in medicine encounter. He thought that the remedy lay in the hands of the examiners, teachers and editors. Examiners should refuse to pass candidates who could not write plain English, and editors should ruthlessly exclude an ambiguous or prolix paper. This of course will raise the question whether an illiterate doctor is also a bad doctor. Sir George would no doubt retort that muddled writing means muddled thinking, and muddled thinking is not conducive to good diagnosis or intelligent treatment.

THE G.P. AND THE HOSPITAL

Every reader of this journal must by now be aware of the sad dichotomy between general practice and hospital medicine in the N.H.S. It will be recalled that some months ago the Platt committee made certain recommendations for the employment of general practitioners in British hospitals, from most of which they have been rigidly excluded in recent years. A B.M.A. committee has now examined these proposals and commented on them. This committee naturally welcomes any efforts to get the G.P. back into the hospital, but it wants to ensure that general practitioners who do enter hospital shall be treated fairly and not just given menial tasks. The committee wishes to ensure that they shall have the full clinical responsibility that is theirs in their own practice, and that they will have proper status and security of tenure. The committee warns that trying to solve the medical manpower shortage by inducing young doctors to stay in hospital posts longer may simply deplete the pool of G.P's and in the end help nobody. One thing the committee sets its face against is the rather mean arrangement by which when a G.P. works in a hospital his remuneration should be deducted from the pool available to pay all the G.P.'s in the area for their work outside hospitals.

A CHANGE IN DIRECTION

One of the personalities in B.M.A. circles who is well known outside this island is Dr. Solomon Wand of Birmingham. He has been connected with B.M.A. committees for more years than his colleagues can recall, and has been Chairman of the B.M.A. Council since 1956, after a period of pitched battle with government as chairman of the General Medical Services Committee, which represents the interests of all the general practitioners working in the N.H.S. Dr. Wand has now hung up his weapons and retired from the direction of B.M.A. affairs to as peaceful an existence as it is possible for a man of his immense energy and elasticity to lead. In addition to his B.M.A. work, Dr. Wand was elected chairman of a World Medical Association study committee set up by the Assembly of that body two years ago in Montreal, when some dissatisfaction with the trends in the association was expressed. Dr. Wand and his committee then produced enough ideas to last the association for the next decade at least, and in Rio de Janeiro this September he and his colleagues were thanked for their work and allowed to suspend their activities until the Council of the W.M.A. had had time to digest just a few of the recommendations of the Wand committee. It is hard to believe that this indefatigable worker in the cause of organized medicine will not find some further outlet for his energies and his negotiating skill.

Meanwhile, the new Chairman of Council of the B.M.A. is also not unknown to Canadians. Dr. Ian Grant has visited Canada more than once, and was a guest lecturer at the annual convention of the College of General Practice two or three years back, when he entertained a large audience with a colourful description of the medical services in a small Arab kingdom. Dr. Grant, a general practitioner in Scotland, is the fourth representative of that branch of medicine to occupy this high place in the Association, and it is fitting that he should also have been elected to the Council of the W.M.A. at its recent Assembly in Rio.

THE FIVE-DAY WARD

At a busy hospital in the Midlands, the Leicester Royal Infirmary, an experiment is to be tried with the five-day ward. This ward will be open only from Monday to Friday inclusive, and it is hoped that nursing staff may be found who will be willing to work a five-day week and keep it open. This hospital already had to close down wards for lack of staff, and the present idea is that surgeons should review their waiting lists and admit to the new ward patients suitable for short-stay operative treatment, and with home circumstances favourable to early discharge. Indeed some may require only a day or two in hospital. To begin with, only men will be admitted because it is easier to care for convalescent men at home; naturally, if some complication prevents discharge on a Friday, the patient will have to be moved to a full-time ward. The co-operation of the general practitioners is being secured, and they are going to be asked beforehand whether they know of any barrier to a patient's admission to the short-term ward.

S. S. B. GILDER

MEDICAL MEETINGS

CANADIAN ASSOCIATION OF PATHOLOGISTS

The thirteenth annual scientific and business meeting of the Canadian Association of Pathologists was held in Montreal, June 22 to 24, 1961.

The Association, consisting of a membership of 273, was founded in 1949. A number of Provincial Associations of Pathologists had been active for many years prior to this date. During the first few years most of the efforts of the Canadian Association of Pathologists were directed towards organizational issues and the numerous current problems facing Canadian pathologists. Increasing emphasis is now being given to scientific activities, research, teaching, and standards of practice.

The scientific program of the 13th annual meeting was a joint meeting of the Canadian Association of Pathologists and the Quebec Association of Laboratory Physicians and Pathologists. Fourteen scientific papers plus four papers on quality and quality control were presented. The guest speaker was Dr. Edward A. Gall, Professor of Pathology, University of Cincinnati, who gave an excellent paper entitled "Pathogenetic Patterns in Cirrhosis of the Liver". The scientific papers were very well received by the more than 100 pathologists in attendance. The quality and scope of these papers leave no doubt that pathologists in Canada have become of age and are making a real scientific contribution.

The business meeting dealt with numerous problems, some very urgent. The following officers were elected: Past President, Dr. H. G. Pritzker; President, Dr. F. W. Wiglesworth; Eastern Vice-President, Dr. René Lefebvre; Western Vice-President, Dr. J. M. Lederman; and Secretary-Treasurer, Dr. D. W. Penner. Sixty-two new members were approved.

A number of committees have been very active during the past year in dealing with various problems:

Committee on Cytology. There has been a very marked increase in the use of cytology. In order to evaluate better the problems and facilities across Canada a survey was conducted. This showed that the demand for and services available varied across Canada. In a number of areas, pathologists have developed cytology as a routine diagnostic service and in many areas facilities have been sufficient to meet the demand. There is, however, a critical shortage of trained cytology technicians and technician-training facilities. In British Columbia there is a well-developed cytologic program which is currently undertaking a mass survey of the entire female population.

The following recommendations were approved:

1. Cytological diagnosis is part of the practice of pathology.

2. The Canadian Association of Pathologists should develop and sponsor a section of cytology within its constitution, to include, as necessary, members of other medical specialties concerning themselves with cytological diagnosis.

3. The Association should encourage and help in every way possible the development and expansion of training facilities for cytological technicians and for pathologists.

4. The Association should encourage development of cytological services by individual pathologists in hospital laboratories. While not advocating or encouraging the development of mass screening programs, the Association should be prepared to cooperate where these are initiated. It should, however, in general set its face against the establishment of centralized laboratories; and where such laboratories are established the Association should regard it as fundamental that they be supervised by a recognized pathologist.

Ad-Hoc Committee on Quality and Quality Control. This Committee was very active during the past year. A survey of Canadian laboratories was conducted to obtain information on the use of quality control and the problems relating to this. Pathologists have for many years been very active in establishing laboratory standards and controls for their professional work. The rapid expansion of laboratories, and the tremendous increase in volume since the advent of the hospitalization and diagnostic services plan, have created many problems. There have been a marked increase in laboratory budgets and an increasing resistance on the part of the government agencies to grant these. The chief problem thus became maintenance of adequate standards in the face of an increasing work-load.

Volume of technical work in laboratories is now being recorded across Canada in terms of unit values. This has required continual revisions and additions, as new and different technical procedures are initiated. Lately there has been an increasing tendency for hospital administrators to attach direct dollar values to these units for the purpose of accounting. Since the professional work load is not included in these unit values, many problems have arisen.

There still remains a shortage of trained medical technologists in Canada. With better salaries and the development of larger training schools, the problem is not nearly as acute as a few years ago. Many problems relating to technicians remain, however, and it was for this reason that Dr. Wiglesworth proposed the following motion to the Canadian Medical Association Council: "That a joint Committee be set up consisting of the Canadian Medical Association and such affiliated specialist societies as are interested in studying the problem of technician education and its relationship to medical services with particular reference to the so-called 'internship'."

Formation of a New Section in Cytology

The constitution of the Canadian Association of Pathologists was modified so that various new sections could be formed. Following this, a formal motion was received from a number of members of the Canadian Association of Pathologists to form a section of cytology. This motion was approved and a small organizational committee was set up to recommend on details, such as the exact name, rules and regulations. It is now possible for any suitably qualified medical doctor who has an interest in the clinical or laboratory aspects of cytology to become an associate member of the Canadian Association of Pathologists and a full member in the cytology section. This should do much to improve and develop cytology in Canada. D. W. PENNER, M.D.

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ASSOCIATION NOTES

THE CREST AND SEAL OF THE CANADIAN MEDICAL ASSOCIATION

A. D. KELLY, M.B.

The careful reader of the Transactions of the 94th Annual Meeting will have noted that the Committee on Public Relations recommended, and the General Council adopted, a proposal for a change in the Association Crest. The instruction was "to have the C.M.A. Crest appropriately altered to include a bilingual interpretation" of the name of The Association. Since our by-laws designate our official name in the French language, the proposal was accepted without incident other than a mild reproof to the General Secretary for referring to our snake on the stick as a Caduceus.

There followed a period of intermittent staff consideration of the problems of design between more momentous duties and it was postulated that the appearance of our insignia should be changed as little as possible, that the bilingual lettering should show the equivalent names quite separately, and that the traditional features should be retained, consistent with the purpose of the new look.

A modest research has failed to establish the origin of the C.M.A. Crest but it is clear that this version was used by our printers on the title page of the Index Number of the *Canadian Medical Association Journal* from its first issue in 1911 until 1953.

The feature of this design is that it is a representation of our Crest in the form of a Seal. It incorporates the staff of Aesculapius with the single snake entwined, head pointing to the viewer's left, the word FOVNDED and the date 1867. The staff, which is usually represented without adornment, sprouts maple leaves in this instance, a deviation which makes the device distinctly Canadian.

It is not proposed to add to the voluminous literature on medical symbolism or to discuss the distinction between the Caduceus of Mercury and the Staff of Aesculapius. Suffice it to say that the originator of the central figure in the C.M.A. Crest was on firm ground when he selected the single serpent entwined on a staff to represent the mythological background of the medical profession.

It is of interest to observe that this earliest representation of our Crest portrays it imbedded in sealing wax. Our Crest has the practical and official use of being affixed to legal documents negotiated by The Canadian Medical Association by means of an embossing Seal. The by-law makes reference to its use in the following words: "The Seal which is now in the hands of the General Secretary shall be the Seal of The Association." Legal opinion had therefore to be sought in respect to the contemplated change, and the inclusion of the word "now" will require a By-law Amendment to regularize our use of a new symbol.

At some undetermined date, probably in the early thirties, a modernization and tidying up of our Crest took place, and the result is reproduced here. Most

observers would agree that the elimination of the representation of a wax impression is an improvement and that the design emerges in a clean and pleasing form. This is the version which appears on our Seal and it has been used on booklets, place cards, programs and other printed material for at least thirty years.

In carrying out the behest of the General Council to produce a new bilingual insignia, it was important to retain insofar as possible the distinctive features of its predecessors and to incorporate certain corrections and improvements. For example, the official name of our Association as stated in our Act of incorporation is **The** Canadian Medical Association and our by-law states the French equivalent to be L'Association Médicale Canadienne. Then too, the word "Founded" in the design, the spelling of which had been previously changed from the Latin "V", appeared to be asymmetrical and redundant, particularly if presented in two languages. It was agreed however that the date of our establishment was important to retain in view of our approaching Centenary. The composite of these considerations was sketched and turned over to a designer of repute who submitted for Executive Committee approval the version here reproduced.

We have not consulted the College of Heralds but we have involved the opinions and the talents of a number of interested persons. It is our hope that the design as now adopted will appeal to the membership as a good one and that the objective of portraying our Association as truly national in respect to both basic cultures will be achieved. The Committee on By-laws will recommend to the 95th Annual Meeting an amendment to our rules and, if adopted, the new Crest and Seal of The Association will go into official use.

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BOOK REVIEWS

CANADIAN CANCER CONFERENCE. Vol. 4. Proceedings of the Fourth Canadian Cancer Research Conference, Honey Harbour, Ontario, June 12-16, 1960. 414 pp. Illust. Academic Press Inc. (London) Ltd., London; Academic Press Inc., New York, 1961. $12.00.

The Canadian Cancer Conference 4 is composed of a collection of papers from the Honey Harbour Conference in June 1960. There are four general sections, the first of which covers in an unrelated fashion cellular biochemistry and physiology. This is of value to workers in this field but is not to be recommended as a reference for inquisitive amateurs.

Dr. Gregory Pincus reports that in a five-year study of artificial menstrual regulation there has been only 1/25th of the expected rate of cancer of the cervix and breast; he speculates upon the value of a constant hormone environment as a method of cancer prophylaxis.

In the section on cell behaviour there are two papers of clinical interest. Dr. Sumner Wood, Jr., gives a dynamic presentation of a study of the production of vascular metastases. He showed that they may be increased by postoperative stress and ineffective radiotherapy or chemotherapy and that a decrease occurs with anticoagulants and effective cancericidal agents.

Dr. A. C. Ritchie demonstrated the presence of tumour cells in the blood of postoperative breast patients; his group feels that this does not affect prognosis.

A section on viral carcinogenesis has several interesting papers. There is a superb and concise paper by Dr. E. A. McCulloch which demonstrates *in vivo* carcinogenesis by the polyoma virus. In addition he speculates upon the interesting analogy with bacterial lysogeny as a possible explanation of the failure to demonstrate virus particles in other tumours of possible viral origin.

The section on chemotherapy was interesting in June 1960 but has now lost most of its punch. Historically it contains the first papers on V.L.B. (vincaleukoblastine) but the clinical reports were very preliminary and have been replaced by more extensive trials. V.L.B. now has an established role in the chemotherapy of Hodgkin's disease and Methotrexate-resistant choriocarcinoma.

A HANDBOOK OF DIFFERENTIAL ORAL DIAGNOSIS. The Postgraduate Dental Lecture Series. 234 pp. The C. V. Mosby Company, St. Louis, Mo., 1961. $6.50.

This book is one of the Postgraduate Dental Lecture Series. According to the preface, it is "an index of signs, symptoms, and diseases, compiled primarily to aid dental practitioners and students in evaluating the many manifestations of disease occurring in the mouth and surrounding structures".

The book is divided into approximately 70 main topics which are arranged alphabetically. Topics include individual diseases, groups of related diseases, signs or symptoms common to many diseases, and anatomic structures subject to a number of diseases. Points relevant to a differential diagnosis are discussed under each topic. An appendix contains a table on the chronology of development of the human dentition, several tables on laboratory test values and one on recommended dietary allowances. There is an index which is very important to the usefulness of such a book. There are no illustrations.

The idea of the book, to bring together and sort out the myriad of signs and symptoms which might stem from either medical or dental pathological conditions, is good. However, the author has used strict medical terminology uncompromisingly in his attempt to be brief in the text. He presupposes an acquaintance with the precise meaning of descriptive medical terms which the reader may not possess. One wonders whether dental practitioners will be able to recall without annoying reference to a dictionary the meaning of words like analeptic, ataractic, connatal, carpopedal, epilation, and hirsutism. A glossary of terms would be appreciated, especially by the dental practitioner who does not use such an extensive vocabulary in his everyday work.

The alphabetical arrangement of the book is satisfactory but of no great advantage since one nearly always ends up using the more detailed index at the back of the book to locate data. This detailed index is excellent except that the numbers in italics (for the main discussion of a subject) are sometimes hard to distinguish from the ordinary numbers.

New books are prone to errors in the text, sometimes humorous errors. A few which caught the eye of this reviewer were lactobaccilli per millimeter instead of milliliter (p. 55), catch scratch for cat scratch (p. 116) and parental for parenteral (p. 57).

The author has gathered and organized a great deal of material in this small volume. With his efficient cross-indexing and succinct text he has given us an illuminated torch with which to explore the diagnostic no-man's land between medicine and dentistry. Used as the author intended it to be used the book is a valuable addition to the medical and dental literature.

THE PHYSIOLOGICAL REGULATION OF SALIVARY SECRETIONS IN MAN. A Study of the Response of Human Salivary Glands to Reflex Stimulation. Alexander C. Kerr. 86 pp. Illust. Pergamon Press Ltd., London; Pergamon Press Inc., New York, 1961. $6.50.

The study of salivary secretion in man has been greatly handicapped by the crudity of the methods used for collecting saliva and stimulating its secretion. This book describes new and elegant methods for measurement of saliva secretion rates from the parotid, submandibular, and sublingual glands in man. The results obtained, although more quantitative than previously obtainable, do not lead to any major new conclusions, and perhaps the most interesting result is the confirmation of Lashley's finding that the thought of food does not stimulate the secretion of saliva and that the sensation of watering at the mouth is purely subjective and is not at all related to the actual rate of secretion of saliva. No doubt but for his untimely death Dr. Kerr would have continued to use these new methods for measurement of the concentrations of electrolytes and other solutes in saliva and also for the study of the action of drugs and hormones. For such studies he has laid a very useful foundation and it is to be hoped that others will continue the work along these lines.

MEDICAL NEWS *in Brief*

(Continued from page 1013)

PEPTIC ULCER: AN IMPORTANT HEALTH PROBLEM

It is estimated that 2,440,000 people in the United States have peptic ulcers, an average of 14.4 per 1000 population. These estimates by the National Health Survey are based on data collected in household interviews during July 1957 to June 1959.

The prevalence rate in the current survey is nearly six times the rate of 2.6 per 1000 reported in the National Health Survey of 1935-36. Much of the recorded increase, however, is probably spurious. With the growth and improvement of diagnostic aids—particularly radiological equipment—in both hospital and private practice, peptic ulcers have been detected with increasing frequency. Another factor may be the refinement of survey techniques used to elicit information on morbidity through household interviews. Then, too, so much publicity has been given to the association of ulcers with the stress of modern life that the condition may in fact be overreported.

The condition is relatively infrequent under age 25, there being only 1.6 cases per 1000 population, but the rate rises sharply with age to 27.6 per 1000 at 35-44 years and to a peak of 28.7 at 45-54. It is only slightly lower in the next 20 years of life, then falls to a considerably lower level at ages 75 and over.

Peptic ulcers are much more frequent among men than among women, the ratio being 3 to 1 at all ages combined. The sex ratio of cases is particularly high—4 to 1—at ages 25-34, and then declines irregularly with advance in age.

The amount of disability attributable to peptic ulcers is considerable. According to the National Health Survey, ulcers caused an average of 19.3 days of restricted activity a year among persons with the disease. About one-fourth of all persons with ulcers reported bed disability of one or more days a year on account of the condition; of this group, about two-thirds were confined to bed seven or more days a year. Peptic ulcers are also responsible for the loss of a great deal of working time. Thus, among persons aged 17 and over, about 50,000 were absent on an average working day because of ulcers. In each of the survey years, 12 million days were lost from work, or about 7½ days per person; at ages 45-64 the average time lost was 11 days a year.

Compared with the frequency of peptic ulcers, the number of deaths attributed to the disease is relatively small. There were about 10,800 such deaths in the United States during 1960, equivalent to a rate of 6 per 100,000 population.

In the past decade, the death rate from ulcers of the stomach has remained virtually stationary while that from ulcers of the duodenum has increased slightly. As a result, the mortality rate from ulcers of the two sites has been about the same in recent years, whereas a decade ago the death rate from stomach ulcers was about one-fourth higher than that from duodenal ulcers.

Among white persons the death rate among males is somewhat over three times that for females at all ages combined; at ages 55-64

(Continued on page 30)

MEDICAL NEWS *in brief*

(Continued from page 29)

the ratio is nearly 5 to 1. In both sexes, the mortality from these conditions is very small under age 35, but thereafter increases progressively with advance in age to a peak at the oldest ages. Ulcers of the stomach and duodenum record a somewhat higher death rate among white than among nonwhite persons at all ages combined, reflecting the markedly higher mortality from the disease among white persons at the older ages.

The wide disparity between the frequency and the mortality from ulcers indicates that the case-fatality rate of the disease is low. In most cases, medical treatment and supervision prove adequate; even in hospitalized cases only about one-third are treated surgically, according to the National Health Survey. Increased efforts are being directed to early detection of patients who are the more likely to need surgery—for example, those who have suffered a hemorrhage. In general, the long-term outlook for people with peptic ulcers is very favourable.—Statistical Bulletin (July 1961), Metropolitan Life Insurance Company.

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BLOOD-MARROW MIXTURES IN IRRADIATED MICE

The effects of blood given to lethally irradiated, marrow-treated mice fall into at least three categories which depend upon the genetic relation between donor and host elements. If donor blood and bone marrow are both isologous to the host mice, early radiation death is prevented and the irradiated mice survive for many months. If the donor bone marrow is homologous and the donor blood is isologous to the host, transplantation does not succeed and the host mice die from marrow failure. If the blood and bone marrow are both homologous to the host mice, but isologous to each other, the recipient mice do not die of marrow failure, but develop what appears to be an accelerated secondary disease with persistence of the transplanted marrow.

A report of a study of these three categories is presented by Goodman and Congdon (*A.M.A. Arch. Path.*, 72: 18, 1961). Two other possible situations where (1) the bone marrow is isologous and blood homologous to the recipient, and (2) the marrow is homologous to the host and blood homologous to both the recipient and the marrow donor, were not examined in this report.

Evidence was produced that a radiosensitive, immunologically competent cell is present in the blood of normal mice which when injected into an irradiated homologous bone marrow-treated mouse causes or contributes to the death of the recipient. If isologous blood cells are employed, death results from rejection of the grafted homologous marrow. When homologous blood is given, however, the marrow graft persists until death of the animal from an exaggerated secondary disease syndrome.

It is presumed that the effective cell in the peripheral blood is the monocyte or large lymphocyte. The

origin of this cell may be in the germinal centres of organized lymphatic tissues, but other sources could not be completely ruled out.

It is suggested that the presence of immunologically active cells from blood contaminating the bone marrow preparations in experiments with large animals might explain some of the difficulties encountered in obtaining recovery from lethal irradiation in these species, including man.

THE FREQUENCY OF PARKINSON'S DISEASE

More than 25,000, and possibly as many as 43,000, new cases of Parkinson's disease are now occurring each year in the U.S., according to a pamphlet recently issued by the National Institute of Neurological Diseases and Blindness of the Public Health Service.

The total number of victims is at least 300,000, the PHS publication states. Furthermore, since the incidence of the disease increases sharply when people pass the age of 50, and since the number of older people in the U.S.A. is steadily increasing, both new cases and total number of Parkinson's disease patients are likely to increase unless a preventive can be found.

"Parkinson's Disease — Hope Through Research" is listed as Public Health Service Publication No. 811 and Health Information Series No. 100. Single copies may be obtained without charge from the Public Health Service. Write the Superintendent of Documents, Government Printing Office, Washington 25, D.C.

AMERICAN COLLEGE OF ALLERGISTS

The American College of Allergists Graduate Instructional Course and Eighteenth Annual Congress will be held April 1 to 6, 1962, in the Hotel Radisson, Minneapolis, Minn. For further information, write to: John D. Gillaspie, M.D., Treasurer, 2141 14th Street, Boulder, Colo.

ANTIBODY TO POLIOVIRUS IN A WELL-IMMUNIZED COMMUNITY

In County Down in 1960 a poliovirus antibody survey was undertaken by Dane and Dick (*Lancet*, 1: 1217, 1961) among 270 children under 16 years of age. An estimated 95% of them had received three doses of vaccine.

Immunity to type II and type III virus appeared to be satisfactory: 99% had antibody to type II virus, and 94% to type III. In younger children the proportion immune to type I virus was significantly lower; only 72% in the one-to-five year age group had circulating antibody, compared with 98% of older children.

In the one-to-five year age group 94% tested within a year of receiving the third dose of vaccine had antibody to type I virus, compared with 64% of children tested more than one year after the third dose.

For younger children a fourth dose of vaccine seems desirable. It should be given about one year after the third, to boost their immunity to type I virus.

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Nov. 4, 1961, vol. 85

PROVINCIAL NEWS

BRITISH COLUMBIA

The University of British Columbia opened its Physical Medicine Therapy School in September. Dr. Brock Fahrni is Director of the School, assisted by Miss Margaret Hood as Supervisor of Occupational Therapy, and Miss Jane Hudson who will supervise physiotherapy training.

Dr. Fahrni says that the object of the course is to provide well-trained therapists who, with the doctor and nurse, will be the third member of the team at hospital, rehabilitation centre, outpatient and home levels.

The course consists of two academic years at the University of British Columbia and a third rotating supervised intern year. After two or more years of practice, a third academic year may be taken, leading to a bachelor's degree.

The Chris Spencer Foundation has donated $6000 to the Health Centre for children at the Vancouver General Hospital, to be used in research into the cause and cure of glandular disturbances in children.

This Foundation was established in memory of the late Chris Spencer, a well-known and well-loved pioneer merchant of British Columbia who died in 1953. He was very intimately concerned in many public benefactions during his lifetime.

Dr. George R. Kerr, formerly at the Health Centre, who has been away for some years, actively engaged in endocrinological work, will be in charge of the Centre's research program. Dr. Kerr has returned to Vancouver and is attached to the Department of Pediatrics, University of British Columbia.

At the Annual Meeting of the College of Physicians and Surgeons of B.C. at Kamloops, October 3 to 6, the speaker was the Hon. P. A. Gaglardi, Provincial Minister of Highways.

Dr. G. F. Amyot, Provincial Deputy Minister of Health, will receive an honorary degree from the University of British Columbia at its Fall Convocation on October 26. Dr. Amyot has been Senior Medical Health Officer of British Columbia since about 1940, succeeding Dr. Esson Youn, and has also served as Canadian delegate to the World Health Organization (1948).

Dr. Myron M. Weaver, who was the first Dean of Medicine at the University of British Columbia, will also receive an honorary degree on the same occasion. Dr. Weaver made an outstanding contribution as Dean of Medicine, and his hard work and organizing ability put the medical school definitely in the first rank of Canadian medical schools. He is at present Dean of Graduate Studies at Union College, Schenectady, New York.

Dr. J. F. McCreary, Dean of the Faculty of Medicine at the University of British Columbia, has announced that the design of the proposed University Hospital in Vancouver is now under intensive study. The planners have visited every hospital built in Europe and North America since the end of the Second World War. The hospital will be small, but ultramodern; it will have 310 acute beds, 60 psychiatric beds and 40 chronic beds. Working drawings will be prepared in 1962. Construction will take three years.

Dr. A. John Nelson, Medical Director of the B.C. Electric Corporation, has left for Yugoslavia to attend a meeting of the International Epidemiology Association.

J. H. MACDERMOT

SASKATCHEWAN

A Cytological Research Laboratory is being set up in the Munroe Wing of the Regina General Hospital.

A conference for the interpretation of the Canadian Nurses' School Improvement Program was held at Ellis Hall, University of Saskatchewan, on September 21 and 22.

Dr. C. L. Tisdale of Prince Albert was elected to the office of Governor at the Western Canadian District Kiwanis convention, held recently in Medicine Hat, Alberta.

ONTARIO

Weekly medical broadcasts by 22 different members of the Essex County Medical Society were presented over station CBE, Windsor, from February 1 to June 26. Among the subjects discussed were: "Behaviour Patterns in Children", "Natural Childbirth", "Psychosomatic Diseases", "High Blood Pressure", "Wonder Drugs" and "Are X-rays Dangerous?"

Northwestern General Hospital, Toronto, has opened a wing of four floors containing 171 beds, bringing the hospital's bed total to 275. The cost of this addition is about $1,100,000, of which the Federal Government provided $354,000 and the Provincial Government $380,270. The municipality of North York and the hospital board must meet the balance of the cost. The Hon. Matthew B. Dymond, Minister of Health, officiated at the opening of the hospital addition.

LILLIAN A. CHASE

A Scleral Contact Lens Department has been opened at the Toronto Western Hospital under the auspices of the University of Toronto. Its purpose is to help those who are not aided by ordinary spectacles and to give protection or cover cosmetic blemishes. It will not supply lenses to patients simply desiring to avoid the wearing of spectacles.

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ABSTRACTS

MEDICINE

Obesity in Men: A Clinical Study of Twenty-five Cases.

M. MENDELSON, N. WEINBERG AND A. J. STUNKARD: *Ann. Int. Med.*, 54: 660, 1961.

Twenty-five obese males, admitted to the medical and psychiatric clinics of a large American hospital, were studied by a variety of clinical techniques to determine the etiology of their obesity, the differences in their dietary habits, and the possible differences between the obesity of these individuals as an integrated group and the obesity of females also as an integrated group. A marked variability of habits was observed in these males, and no common type of personality was noted which would distinguish them from the non-obese males. However, two types of obese males could be distinguished according to the age of appearance of the obesity. The subjects in whom obesity had commenced before the attainment of their adult state were heavier, had more unstable weight careers, and had higher levels of intelligence than the subjects who had become obese as adults. Furthermore the obesity of the subjects with "juvenile obesity" frequently coloured their concepts of themselves and their bodies in a most derogatory manner. This was not the case among the 14 males with "adult obesity".

In contrast to the relation between the ingestion of alcohol and the presence of obesity in females, this factor had a more important role and inactivity a less important role in the case of obese males. S. J. SHANE

Hepatoma: Clinical Experiences with a Frequently Bizarre Tumour.

E. J. BENNER AND D. H. LABBY: *Ann. Int. Med.*, 54: 620, 1961.

In 47 cases of primary carcinoma of the liver, 14 of the patients (30%) presented clinical pictures dominated by aspects which, in the past, were considered to be atypical or rare. Nine cases with clinical courses of an atypical, protean and polymorphic character are discussed in detail to emphasize the fact that, in cases of primary cancer of the liver, the clinician finds himself frequently confronted with mystifying clinical pictures. A discussion of the signs and symptoms, based on intrahepatic growth patterns and the extrahepatic dissemination of the tumour, is presented to assist the clinician in the development of a systematic pathophysiologic background that will enable him to diagnose the bizarre aspects of the tumour. The fact is reemphasized that cirrhosis and hepatoma are frequently associated. Observations are cited that may indicate the possibility of an increasing incidence of hepatoma in the United States. Changes in the current concepts of the association of posthepatic and postnecrotic cirrhosis are also discussed.

The figures for morbidity from infectious hepatitis are presented, and it is emphasized that there has been an alarming increase in the incidence of this disease. Emphasis is also placed on the increase that one may expect in the incidence of one of its complications. It is noted in this connection that hepatomas have developed in 14% of a series of 221 cases of postnecrotic cirrhosis. S. J. SHANE

Diagnosis and Treatment of Lupus Erythematosus, Dermatomyositis, and Scleroderma, with Emphasis on Cutaneous Findings.

R. K. WINKELMANN: *J. Chron. Dis.*, 13: 401, 1961.

A brief review of the diagnosis and treatment of lupus erythematosus, dermatomyositis and scleroderma is presented. The cutaneous findings in these three conditions are distinctive features and aid in the clinical diagnosis. However, Raynaud's phenomenon may occur in all three diseases, and sclerosis has been associated with each. Thus, it is the pattern of the individual lesions and their correlation with the course of the disease that are of diagnostic usefulness. In each instance, clinical and laboratory evaluation of the case will indicate the true nature of the primary process.

The treatment of these three diseases is entirely different: antimalarial compounds are of no value in the treatment of dermatomyositis or scleroderma of the generalized type; steroids help the inflammatory changes in dermatomyositis and systemic lupus erythematosus, but do not materially affect any phase of scleroderma; at present, chelation appears to be useful only in the slowly progressive or edematous acrosclerotic form of scleroderma.

The causes of these three conditions are unknown, but it is apparent that the basic mechanisms of these diseases are different and that the tissue reactions are widely separated, judging from clinical and laboratory evidence. Close attention to the cutaneous findings in these diseases may allow earlier recognition of the primary process so that appropriate treatment may be given. FRANCES LETTAU

Atrial Infarction of the Heart.

C. K. LIU, G. GREENSPAN AND R. T. PICCIRILLO: *Circulation*, 23: 331, 1961.

In six cases of atrial infarction associated with ventricular infarction, all were diagnosed ante mortem and confirmed by autopsy. Atrial infarction should be suspected in patients with ventricular myocardial infarction who have any form of atrial arrhythmia. Frequent electrocardiograms should be obtained, especially if sinus rhythm has just been re-established after episodes of supraventricular tachycardia or atrial fibrillation. The major electrocardiographic criteria for the diagnosis of atrial infarction are elevation of the P-Ta segment of over 0.5 mm. in V_5 and V_6 with reciprocal depression of the same segment in V_1 and V_2; elevation of the P-Ta segment of over 0.5 mm. in lead I and its depression in leads II or III; depression of the P-Ta segment of more than 1.5 mm. in precordial leads and 1.2 mm. in leads I, II and III in the presence of any form of atrial arrhythmia. The minor electrocardiographic criteria in making the diagnosis of atrial infarction are: abnormal P waves, M-shaped, W-shaped, irregular or notched. A diagnosis of atrial infarction can sometimes be made when the presence of ventricular myocardial infarction cannot be definitely established by electrocardiogram. The treatment of atrial infarction is similar to that of ventricular infarction. Attention should be directed to the control of atrial arrhythmias and to the prevention of mural thrombi.

S. J. SHANE

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